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CLINICAL IMPRESSIONS OF AN EPIDEMIC OF SANDFLY FEVER IN PALESTINE DURING 1940.

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and

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SANDFLY FEVER, caused by a virus of the dengue variety, though in itself an entirely non-serious disease, may be of considerable military importance. Its incidence in an unprotected population may be very high, and the incapacity it causes, though brief, is often considerable. Therefore an account of its clinical features is of some interest.

During the greater part of the summer of 1940, of the troops concentrated in southern Palestine, only a negligible percentage of the Australian Imperial Force had had an opportunity of acquiring immunity to this virus. No figures can be given as to the proportion of cases occurring among the military population. Many mild cases occurred, in which the man was not prevented from carrying on with his work; many other patients recovered quickly without going to hospital; and the remaining patients needed only a couple of days in a camp reception station. In addition, the First Australian Casualty Clearing Station handled about 200 patients with sandfly fever during a period of two months. The number of patients who were admitted to the First Australian General Hospital suffering from sandfly fever is shown in Table I (see also Figure I).

TABLE I.

Month.	Patients Admitted with Sandfly Fever.	Total Number of Patients Admitted to the Hospital.	Percentage of Total Admissions.
May	1	782	0.1
June	14	740	1.9
July	179	878	20.0
August	383	1,183	31.0
September	190	764	25.0
October	150	1,058	14.0
November	29	839	9.0
Total	946	6,244	15.0

These numbers do not represent the total number of patients observed in hospital suffering from sandfly fever, for there were many who contracted the disease while in hospital under treatment for other conditions. In all, it is probable that some 1,500 patients with the disease were seen in this hospital from May till November, 1940.

Onset and Prodromata.

Two groups of cases were noted: (i) those in which the onset was sudden and there were no obvious prodromata; (ii) those in which prodromal symptoms were present over a period of about twenty-four to forty-eight hours or even more. In the latter the outstanding symptoms were headache, aching limbs, pain in the back, anorexia and a rather striking malaise, of which the most prominent feature was a feeling of great heaviness and weariness. In both types of onset shivering was not uncommon, but this was usually of minor degree. A definite rigor occurred in a few cases only. Sweating

not infrequently accompanied the rise of temperature in the early stages. In a few cases collapse occurred when the onset was sudden or when the patient persisted in trying to continue work; but this never caused anxiety.

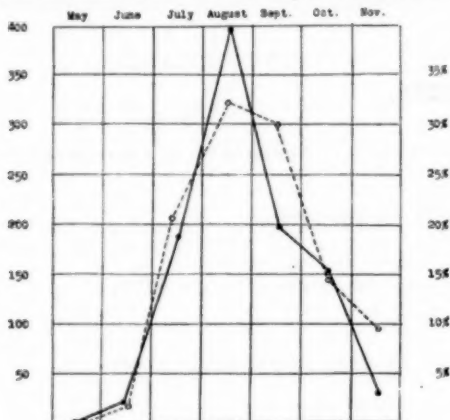


FIGURE I.

Number of patients admitted to hospital suffering from sandfly fever shown thus —; sandfly fever admissions as percentage of total admissions shown thus ----.

Signs.

The General Aspect.

There is a typical facies, which is seen in many of the declared cases and in practically all severe cases. In fact, the "sandfly fever face" is pathognomonic when it is present. The face appears puffy and swollen, and the complexion is uniformly flushed and red. The appearance of thinner persons may superficially suggest well-being, though suffusion of the eyes, when present, readily corrects such an impression. The heaviness and drowsiness of the patients are obvious.

The Eyes.

Conjunctival congestion is very common. In the classical case the conjunctivae are red right up to the limbus, owing to intense engorgement of the superficial small blood vessels, which may be seen in a close dendriform pattern just below the surface. Deeper ciliary congestion was not observed in this series of cases. The eyeballs are almost always tender to pressure, and pain is readily produced by ocular movements. This results in a rather characteristic reluctance of the patient to move the eyes. Photophobia is also common, but bears no essential relation to the degree of conjunctival congestion.

The Mouth and Throat.

The tongue is furred, but in uncomplicated cases no obvious injection of the fauces is seen. One common and striking finding is the presence of a crop of vesicles on the palate. This was an almost constant feature in the epidemic, and being present in the early stages, was a help in diagnosis. These vesicles are entirely different from the granular outcrop seen on the palate and pharynx in some infections of the upper respiratory tract. They extend from the junction of the soft and hard palates back in a triangular area whose base extends across the top of the uvula to the faucial pillars on each side. There is an entire absence of any inflammatory reaction in the mucosa at the base of the vesicles, which are tiny, clear and glistening. They are not seen on any part of the buccal mucous membrane. It is not suggested that this vesicular eruption is peculiar to sandfly fever. It appears rather to be a feature of a number of virus infections as contrasted with other infections. It was a matter of considerable interest to us to observe that an identical eruption on the palate was found in cases of infective hepatitis—that is, infectious non-leptospiroid jaundice. This disease is endemic in Palestine, and a number of men

suffering from it were admitted to hospital during the epidemic of sandfly fever. We were also impressed with the occurrence in these cases of tenderness of the eyeballs and of pain on ocular movement, and we conclude that these signs, together with the palatal eruption, tend to support the hypothesis that infective hepatitis is a virus disease.

Herpes labialis, so common in many other infections, especially in coccal infections of the respiratory tract, was not observed in any case. Catarrhal signs in the nose and throat were absent in uncomplicated cases. In the later phases of the epidemic, during a period when it happened that respiratory tract infections were fairly common, it was thought that sandfly fever seemed to have some synergic influence in slightly intensifying pre-existing catarrhal symptoms. The effect was only transitory and subsided with the fever.

The Skin.

While the face is curiously red and puffy, the skin of the body is frequently white and clear, though it may feel pungently hot. Occasionally an erythematous flush was seen on the trunk, particularly on the skin of the abdominal wall; but no true morbilliform rashes were encountered. In three cases a papular rash, somewhat like that of very early measles, was found on the trunk.

Sandfly bites were not always seen on the exposed parts. Some persons are intensely allergic to the bite of the sandfly; but the formation of irritable lumps at the site of the bites is a phenomenon quite apart from susceptibility to the virus conveyed by the insect. As might be expected, therefore, no connexion whatever was observed between the occurrence of painful sandfly bites and the appearance of sandfly fever.

Sweating was very common during the febrile period.

Temperature.

Fever was usually of moderate degree. In a random series of 50 cases the maximum temperature was 104° F., and this occurred in 2% of the cases only. In 6% the temperature reached 103° F., and on the average its greatest height was 102.5° F. Fever lasted over three days in more than 90% of the cases in this series. The name "three days fever" may aptly describe many of the mild cases, but in general is not strictly accurate.

The type of temperature curve most usually recorded is shown in Figure II. In cases in which the fever lasted a little longer, a curve such as that shown in Figure III was common. Secondary rises of temperature occurred

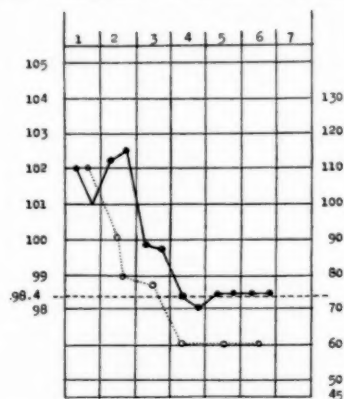


FIGURE II.

Temperature —; pulse rate ----.

at variable intervals in a number of cases. Sometimes the fever recurred after several days and was accompanied by a recrudescence of symptoms. This is illustrated in Figure V. In a few cases patients have been on the verge of discharge from hospital or, as in the case of one medical officer, they have been actually discharged when

a second bout has occurred. Such secondary rises in temperature may be suspected of being more likely to occur in cases in which symptoms persist, such as headache, or tenderness of the eyes on pressure or movement. In general it was found useful to regard the infection as being still active while such symptoms and signs were persistent; these indications were used as a guide to the amount of rest needed by individual patients.

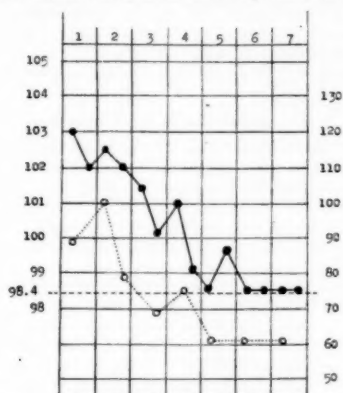


FIGURE III.
Temperature —; pulse rate

Pulse Rate.

A relative bradycardia in sandfly fever is practically always present. The pulse rate at the onset of the disease is often rapid and in proportion to the temperature; but this relation is not maintained, and usually the pulse rate falls more rapidly than the temperature. This is well seen in Figure II. By the second day the pulse rate is usually slowing down by comparison with the temperature, as shown in Figure III. Figure IV illustrates well how the decrease in pulse rate as it were "races" the fall in temperature. This graph and Figure V also show the absolute bradycardia that is frequently a striking feature of the disease towards the close of the febrile period. In a series of cases, by the time the temperature became normal the average pulse rate was 60 per minute. A rate of 50 or even less was often found, sometimes lasting several days into convalescence.

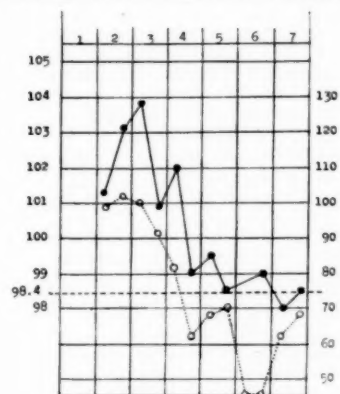


FIGURE IV.
Temperature —; pulse rate

Lymphatic Glands.

We have not seen enlargement of cervical or other lymphatic glands in any uncomplicated case. Some observers hold that swelling of the cervical lymph glands occurred in this epidemic; but in all cases in which we have seen such a swelling, there has been some other reason for its presence. Glandular swellings have not

been uncommon among troops in Palestine, being associated either with rubella or with superficial abrasions of the skin or mucous membrane. Moreover, quite apart from these conditions, throughout the year there have occurred cases of an indefinite febrile illness, which resembled glandular fever, but which was unassociated with mononucleosis. The coexistence of certain infections of the upper respiratory tract during part of the sandfly fever period also caused some confusion in diagnosis.

The Spleen.

In a small percentage of cases the spleen was palpable. It was not tender. The presence of splenic enlargement has been checked by careful observation. There is no doubt that it occurs, though it is but transient and disappears in a few days. Malaria has been excluded in such cases by careful blood examination.

The Gastro-Intestinal System.

Anorexia was a very constant feature. Nausea occasionally occurred, as also did vomiting. A small percentage of patients were admitted to hospital with a mild degree of diarrhoea, and within twenty-four to forty-eight hours it was recognized that they were suffering from sandfly fever. In the later period of the epidemic diarrhoea also occurred during the period of defervescence. Gastro-intestinal disturbances were rather more common among the sandfly fever patients during the latter months of

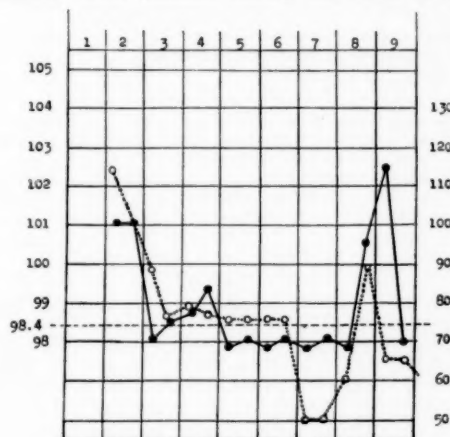


FIGURE V.
Temperature —; pulse rate

summer. This appears to have been due merely to a variant of the manifestations of the disease, for examinations of the stools carried out in several cases of diarrhoea of this kind revealed no evidence of any dysenteric process.

The Nervous System.

Drowsiness and heaviness are extremely common during the day, but nocturnal restlessness is very frequent. The patients themselves often had the impression that the aching of the back and limbs prevented them from sleeping; but these pains were equally complained of during their waking periods throughout the day. Insomnia persisted for several nights in a small number of cases.

No signs of meningeal irritation were seen in any case. A very doubtful spine sign with some slight resistance of the neck muscles was found in a few cases; but this was probably due only to the pain in the muscles.

Hyperaesthesia of the skin over the trunk was not infrequently present. The most common sites were the lower part of the throat and the upper part of the abdomen. There appears to be a connexion in some cases between this objective finding and a feeling of constriction complained of in the same region; but this relation was by no means constant.

Subjective Symptoms.

Headache is very common and varies greatly in degree and type. It is more usually frontal in distribution and is often complained of in conjunction with pain in or behind the eyes. Headache was sometimes intense in this series of cases. It was aggravated by any movement or by straining, particularly by coughing or defecation. Pain on movement of the eyes is often a prominent feature. Dizziness is common. Occurring early in the disease, it is seldom troublesome; but during convalescence it may amount to giddiness, in which there is a component of instability, but no sense of external rotation.

Pain in the back and limbs is invariable and may be troublesome for several days. The pain tends to concentrate in certain places, such as under the shoulders and round the lower part of the chest. It may vanish from one site, only to reappear soon afterwards, and this quality, together with the occurrence of shooting pains in the limbs, caused some of the medical patients to refer to them jocularly as "lightning pains".

A sense of constriction as by a band round the lower part of the thorax or in the neighbourhood of the tenth thoracic segment was a striking feature of many of our cases, particularly in the earlier part of the series. In fact this symptom was so curiously prominent in a number of these early cases that it was reminiscent of the epidemic pleurodynia known as "Bornholm disease". Tenderness of the skin of the trunk has been referred to earlier; it was a transitory symptom as a rule.

Patients suffering from sandfly fever feel very languid and often depressed during the febrile stage.

The Blood Picture.

Pressure of work prevented close study of the blood. In general the results conform to those described as characteristic in fevers of the dengue type. Neutropenia—that is, an absolute diminution of the number of neutrophile leucocytes—is the typical finding, and this occurred in the majority of cases in which differential leucocyte counts were made.

Differential Diagnosis.

Dengue fever might coexist in a community if both mosquito and sandfly vectors were present and infected with the appropriate viruses. The question did not arise in Palestine, but the more severe nature of mosquito dengue fever may be pointed out, as well as the greater prevalence of skin rashes.

Influenza and the Upper Respiratory Tract Infections.

The absence of catarrhal symptoms is the most striking point. When a person already suffering from an infection of the upper respiratory tract develops sandfly fever, some confusion may occur, unless the distinctive clinical picture, as described earlier, is present. It has been observed in most cases during the local military epidemic of these catarrhal respiratory infections that râles at the bases of the lungs are commonly found, even though no extension of pulmonary signs occurs subsequently. Sandfly fever, while causing a general disturbance like that of true influenza and other respiratory infections due to viruses, causes *per se* no special respiratory signs or symptoms. Patients in the early febrile stages of sandfly fever, especially if the temperature is high and if they are exposed to disturbance or exertion, may exhibit a kind of panting, rapid respiration. This is transitory and not related to a true respiratory infection. It must be admitted, however, that in a small group of cases the differential diagnosis of this group of infections from sandfly fever is difficult.

Exanthemata.

The absence of skin rashes and of exanthemata, with the exception of the characteristic palatal vesicles, is distinctive, though measles in the very early stages may cause difficulty in diagnosis.

Malaria.

It is most important not to overlook the possibility of malaria during the height of an epidemic of sandfly fever. Mild malaria has in our experience been diagnosed as sandfly fever. But although certain clinical distinctions between the two diseases might be pointed out, such as the aspect and the greater frequency and severity of rigors in malaria, it must be emphasized that these are not reliable criteria. There is only one trustworthy method, that of examining a blood film. In all doubtful cases a blood film should be made at once; if this is not done in a malarious country, mistakes will certainly be made.

Phenomena of Convalescence.

There do not appear to be any true sequelæ of sandfly fever. Lassitude and physical and mental incapacity are constant to a variable degree during the recovery period after all but the mildest attacks. The average patient in hospital was often allowed out of bed the day after his temperature became normal, and was discharged from hospital about two days later if he was well enough. Even then it was found advisable to recommend two days of light duty. Thus in most cases eight to ten days elapsed after the man's admission to hospital before he was approximately fit. We feel that it is doubtful whether a soldier could undertake duties requiring any high degree of exertion and endurance in less than a week after a sharp attack of sandfly fever requiring his admission to hospital. It will be seen that the disease is by no means negligible from the military point of view, for its infectivity rate is high in epidemics among unprotected people, and it is, temporarily at least, disabling.

Mental depression was a distinct feature of convalescence in some cases; this was not merely apathy, but a positive and more or less distressing pessimism. Syncope was observed in several of the more severe cases when the patient first got out of bed; it was never alarming and did not recur. Giddiness was complained of by many patients during the first few days of convalescence. In a few cases definite unsteadiness was described by the patients. In one case acute toxic labyrinthitis occurred several days after the subsidence of the fever; this was associated with the usual concomitants of nystagmus, vomiting and a sense of rotation of external objects, and was not due to other aural disease. The cause was unknown, and it is possible that it may have been a sequel of sandfly fever. It was noticeable that no patients looked well for at least a week after an attack of average severity. Many appeared pale and dispirited; but full health was usually regained quite quickly once this phase had passed—in fact there seems a kind of turning point in convalescence after which full recovery is rapid.

Recurrences.

Recurrence is unusual soon after a primary attack, but that there are recurrences is undoubted. A second attack was observed in this epidemic within several weeks and months in some instances. These cases have been verified by us, and we are quite certain of the identity of the attacks. The frequency of recurrence has probably been exaggerated, since there has been a tendency, especially among lay observers, to regard every indisposition as due to the prevalent fever. We have not seen one patient have more than two attacks during this epidemic. The second attack was sometimes milder than the first; but this was not invariably so, for in several of our cases a two-day fever with mild symptoms was followed later by a four- or five-day fever with more severe symptoms.

Treatment.

There is no specific treatment. The hospital routine was the administration of a mixture containing aspirin, phenacetin and caffeine, which was fairly effective in relieving the discomforts. A dose of Dover's powder at night was occasionally advisable. Otherwise treatment requires nothing but that the patient shall stay in bed.

Prophylaxis.

It is stated that a reasonable degree of immunity follows an attack of sandfly fever. Even if this is so, it does not dispose of the problem presented by the settling of fresh populations in infected areas. The sandfly is so small and unobtrusive, except in its actual attack, that it is difficult to see and more difficult to counter. Its habit of haunting enclosed spaces accounts no doubt for many infections, and possibly these might be reduced by the spraying of tents and dwellings or mess huts towards dark. But it is the breeding grounds that are difficult to banish, and when a circumscribed area of ground is disturbed by the activities incident upon the housing of a large number of troops, it is not easy to suggest a remedy. It was noticeable that many cases came from certain areas. We feel that the breeding of sandflies was considerably favoured by certain activities throughout the military areas of southern Palestine. The moving of units, pitching of additional tents, erection of new buildings, dispersal of living quarters, excavation of tent floors and raising of parapets for passive air defence, and later the raising of tent floors again in preparation for the wet season—all these manœuvres provided potential breeding grounds. Our hospital site was obviously an admirable site for the housekeeping and family raising of many generations of sandflies. Even here some areas appeared worse than others, and secondary cases occurring in certain wards where patients with other maladies were being treated, often came in waves. There seemed reason to believe that the sequence was as follows. A few cases would occur in an area known to be infected with sandflies. Suddenly the number of local cases would rise after a period, namely, the sum of the period during which the virus becomes transmissible in the sandfly after it has bitten an infected person, and the period of incubation in the human subject. As successive generations of infected sandflies became available to spread the disease, so its incidence increased.

It is probable that the blackout conditions contributed somewhat to the spread of the fever, for the warmth indoors at night drove many men outside to sit in the dark on or near the ground. Thus they were bitten by the flies before they retired to the protection of their nets during the hours of sleep. Sandfly nets are, of course, a great potential protection, but the net must be of very fine mesh. In civil life it is probably not so difficult to keep one's home and living and sleeping quarters relatively free from sandflies; but in the army the problem is much more difficult. It will be seen that even though the *Phlebotomus* is a night biter only, and though the general issue of nets may give protection during the hours of sleep, these considerations do not offer anything approaching a complete solution of the problem of prevention. Nevertheless some effort is better than none, and if some measures can be instituted to minimize the breeding of the flies near living quarters and to discourage their presence in closed spaces, some good may be done. Sandfly fever is not medically important in one sense; but it is a very uncomfortable nuisance, and when a considerable body of men may be involved over a period of several months, it assumes a greater significance.

Summary.

1. An account is given of the signs and symptoms observed in a considerable series of cases of sandfly fever occurring in southern Palestine under military conditions.

2. It is believed that the clinical picture is a distinctive one and worthy of assimilation by those who may need to recognize the disease.

3. Certain features of sandfly fever are pointed out as being present also in the local endemic infective hepatitis; these features are the combination of a vesicular eruption on the palate and tenderness on pressure and pain on movement of the eyes, with variable conjunctival congestion, together with an absence of *herpes febrilis*. These findings have been observed in other virus diseases, and the determination of the frequency might be of interest.

4. The difficulties and possibilities of prophylaxis are briefly discussed.

THYREOTROPIC AND ANTITHYREOTROPIC FACTORS IN SOME TYPES OF THYROID DISEASE.

By A. R. ROBINSON.

(From the Department of Medicine, University of Sydney.¹)

THE ætiological role of the thyreotropic principle of the anterior lobe of the pituitary gland in the production of human hyperthyroidism and exophthalmic goitre has been under discussion since the original suggestion of Loeb and Bassett⁽¹⁾ that it may possess some importance in this respect. The parallelism which exists between human thyreotoxicosis and the changes experimentally induced by administration of thyreotropic hormone to laboratory animals is quite striking, and has been demonstrated for all those effects referable to enhanced thyroid activity. This subject has recently been reviewed by Lambie,⁽²⁾ who has also discussed the extraction and purification, physico-chemical and biological properties, distribution in animal tissues, and mode of action of the thyreotropic hormone.

Clinical studies, even before the isolation of the hormone, in various types of pituitary disease, had indicated a strong presumption that a thyreotropic principle is of special significance in the regulation of thyroid metabolism. More recently the clinical response to the parenteral administration of suitable doses of purified thyreotropic hormone in cases of thyroid and pituitary disease has been studied and is now well established.

A fund of information on this subject is available in the 1938 report of the transactions of the Third International Goiter Conference.⁽³⁾⁽⁴⁾⁽⁵⁾⁽⁷⁾ A recent contribution is that of Harrison,⁽⁷⁾ working in this department, who has also reviewed the literature. The observed effects, some or all of which may be noticed in any one case, are an increase in basal metabolic rate varying from 12% to 36%, a diminution in the blood cholesterol level when this is raised above normal, a swelling of the thyroid gland present only during the period of rising metabolism, and loss of weight, associated with tachycardia, increased perspiration, tremor, weakness, nervousness and occasionally the onset of delayed or suppressed menstruation.

On both clinical and experimental grounds, therefore, the theory that the excess production of thyreotropic hormone is responsible for hyperthyroidism and exophthalmic goitre in man, is rendered very feasible. The hormone can be prepared in purified form from mammalian pituitaries; it has been isolated from human pituitaries by Müller, Eitel and Loeser⁽¹⁸⁾ and Cope,⁽²⁰⁾ although K. W. Thompson⁽¹⁷⁾ states he has been unable to detect any in some thousand specimens obtained from routine autopsies; when injected into animals it reproduces exactly those symptoms and signs of human thyreotoxicosis referable to increased thyroid activity; it is capable of stimulating the human thyroid in hypothyroid states, especially of secondary origin; and its mode of action has been shown to be independent of vascular or nervous connexions of the thyroid (Eitel, Krebs and Loeser⁽¹⁸⁾). But the final link in the chain of proof is lacking, for the presence of thyreotropic hormone in the blood of normal and thyreotoxic subjects has never been satisfactorily proven. If the hormone circulates in the blood, it must be present in low concentration or unrecognizable by the usual methods of biological assay, because it has not been demonstrated unequivocally in the quantities of blood it is possible to inject into test animals. A method of concentrating the hormone from the blood was described by Fellingner,⁽²¹⁾ who claimed that his process made possible the detection of thyreotropic hormone in quantities of blood as small as 10 cubic centimetres, from both normal and thyreotoxic patients. The amount of hormone present in most specimens of thyreotoxic blood was stated to be definitely less than that in normal blood, and this was

¹ This investigation was performed during the tenure of the Marion Clare Reddall Scholarship and was generously aided by a grant from the National Health and Medical Research Council.

assumed to be due either to a depression of thyreotropic hormone formation in the pituitary, or else to the prevention of some essential change in the hormone, normally occurring in the mid-brain, as a result of an increase in the circulating thyreoid hormone.

Cope⁽²⁾ has made a careful study of the question whether demonstrable quantities of thyreotropic hormone in human blood are present or not. Using the process described by Fellingner, he was able to verify the fact that the method made possible the recovery of a large percentage of thyreotropic hormone previously added to human blood, but was unable to demonstrate thyreotropic activity in normal human and animal blood, even when using volumes five times as large as those found active by Fellingner. In the unconcentrated serum from patients suffering from pronounced primary thyreotoxicosis and from two patients with spontaneous myxoedema, Cope was unable to detect the slightest evidence of thyreoid stimulating factors. Indeed, injections of the serum seemed to cause the appearance in the thyroids of the test animals of a more inactive gland than the normal. The belief was expressed that this was due to the depressant effect of large quantities of circulating thyreoid hormone in the serum, and this hypothesis was supported by further experimental observations. Fellingner, on the other hand, had stressed the importance of the separation from the blood to be tested of incidentally occurring thyreoid hormone, and showed that this was achieved in extracts prepared by his method.

It seemed desirable to attempt to repeat the demonstration of the presence of thyreotropic hormone in thyreotoxic blood, which Fellingner claimed to have accomplished, using a similar concentration method.

In this paper such an attempt has been made with five patients suffering from thyreotoxicosis, one patient with untreated spontaneous myxoedema and one patient with hypopituitarism. The range of the observations made has been extended to include examination of the blood for the presence of antithyreotropic substances of the type first described by Collip and Anderson^(3,4) and later investigated by Spence and Witts,⁽⁵⁾ as the demonstration of the presence of such a substance would help to explain the discrepancies in the results so far obtained.

In two cases observations have been made to determine whether thyreotropic hormone in doses causing pronounced clinical manifestations could be detected in the blood soon after administration. In rabbits, Loeser⁽⁶⁾ had demonstrated the rapid disappearance from the blood of intravenously injected thyreotropic hormone. This occurred more rapidly in the normal than in the thyreoidectomized animal, the difference in rate being apparently due to the lower water-output of the latter. Storage of hormone in the organs was not demonstrable. In the present experiments it was desired to observe whether the concentration of thyreotropic hormone in the blood could be raised to a detectable level or whether the same rapid disappearance of the hormone from the blood stream after injection occurred as already proved in animals.

The observations recently reported by Harrison have been extended by parallel studies made on three of the clinical subjects of the response to thyreotropic hormone injections, with regard to the effect on general metabolism and on the blood cholesterol values.

Material and Methods.

Material.

The thyreotropic hormone¹ used in these experiments was a preparation free of gonadotropic, growth and lactogenic principles, standardized to contain 10 Junkmann Schoeller guinea-pig units per milligramme. Its potency was verified at intervals during the experiments. When utilized for injections into human beings, the hormone was subjected to a preliminary sterilization procedure as previously reported (Harrison⁽⁷⁾).

The animals utilized for biological assay consisted of immature guinea-pigs, from the same stock, of both sexes

and weighing 160 to 220 grammes. The diet consisted of a liberal supply of bran, fresh lucerne and water. The room in which the animals were kept was artificially gas-heated during the winter months.

Experimental Procedure.

The demonstration of a reliable technique by which known added quantities of thyreotropic hormone could be recovered from samples of normal human blood was essential.

Much larger quantities of blood than those employed by Fellingner⁽⁸⁾ in his observations were used. An approximate volume of 100 cubic centimetres of blood was taken, and experiments were performed with both whole blood and plasma. It was demonstrated that a considerable proportion of added thyreotropic hormone could be recovered from both whole blood and plasma by a process closely resembling Fellingner's method. Loeser⁽⁶⁾ has demonstrated in the case of intravenously injected hormone that only the plasma exhibits thyreotropic activity. Plasma possesses the additional advantage that it yields a less bulky final powder extract; but inasmuch as it was desired to adhere closely to Fellingner's procedure and it was still found possible to inject into the test animals the entire powder extracted from whole blood, the latter was finally decided upon as the initial source whence the thyreotropic hormone was to be extracted. The concentration process ultimately adopted is described below.

The patients for investigation after admission to hospital were placed on a controlled diet and subjected to the following treatment: (i) Basal metabolism determinations were made twice and sometimes three times a week by the Douglas bag technique under standard conditions. (ii) Blood cholesterol determinations were made with the patients in the fasting condition at the time of the metabolism determinations. One cubic centimetre of blood was dried on filter paper and extracted for one and a half hours with chloroform. The cholesterol content was estimated by the Liebermann-Burchardt method (estimations in duplicate). (iii) When the patients had given three consecutive consistent basal metabolic rate readings, 150 cubic centimetres of blood were withdrawn under local anaesthesia into a 250 cubic centimetre flask, to which 3.8% of citrate solution had been previously added in the proportion of 1:4. The citrated blood was divided as follows: (a) approximately 100 cubic centimetres for concentration of thyreotropic factor; (b) approximately 30 cubic centimetres for preservation and direct biological assay of antithyreotropic factors.

Estimation of the Concentration of Thyreotropic Factor in Whole Blood.—The concentration of thyreotropic factor in the blood was estimated as follows:

One hundred cubic centimetres of test blood were laked by the addition of an equal volume of *aqua destillata*, made up to 40% acetone and allowed to stand overnight at 0° C. The resulting precipitate was centrifuged off, washed, stirred with fresh 40% acetone and recentrifuged. The combined supernatant fluids were made up to 90% acetone to contain 1% ammonium hydroxide, the ammoniacal acetone being added very slowly with subsequent mechanical stirring of the solution for three-quarters of an hour, followed by standing overnight at 0° C. The precipitate thrown down, containing the thyreotropic hormone, was centrifuged off, washed twice with 90% acetone solution and once with pure acetone, and finally dried by filtration through a Buchner funnel, followed by desiccation at reduced pressure over phosphorus pentoxide.

Two animals were used for each powder extract, each animal receiving four or five equal daily doses of the powder (approximately 0.5 gramme) suspended immediately before intraperitoneal injection in two or three cubic centimetres of sterile normal saline solution. The injections were well borne by the test animals, whose progress was noted by daily weighing, and which were sacrificed on the day following the last injection for observation of the thyreoid histology. When, for example, 50 units of thyreotropic hormone were added to 100 cubic centimetres of normal blood, almost the total quantity of hormone could be recovered in the extract as shown by tests on guinea-pigs.

¹ Kindly donated to the Department of Medicine during 1938 by Professor Schoeller, of Schering A.G., Berlin.

Biological Assay of Antithyretrophic Factors in Blood.

For the biological assay of antithyretrophic factors in the blood, 25 to 30 cubic centimetres of whole citrated blood were preserved by the addition of phenol in the proportion of 2.5 cubic centimetres of 10% phenol solution per 100 cubic centimetres of blood, and maintained at 0° C.

The blood was injected intraperitoneally in daily doses of two cubic centimetres into each of two test animals, one of which received in addition two and a half units of standardized thyretrophic hormone and the other five units on the fifth and sixth days. The animals were killed on the seventh day and the thyroids were prepared and examined microscopically, the inhibition of the thyretoid changes normally following injection of the thyretrophic hormone being used as the criterion of the content of antithyretrophic factors.

In the tabulation of the results, slight but definite epithelial changes with corresponding vacuolation, loss of staining and resorption of colloid in the thyretoid gland have been designated "+", more pronounced evidence of activity by "++", and inactive glands by "-" (corresponding to the stages 2-3, 4 and 1, respectively, described by Lambie.⁽¹⁾)

Reports of Cases.

In the following descriptions the results of detailed investigations are shown separately; otherwise the findings are collected into composite tables set out at the conclusion of the clinical data.

CASE I.—Mrs. J.D., aged fifty-five years, suffered from myxedema and diabetes mellitus. She had a history of progressive weakness, breathlessness, palpitation and nocturnal dyspnea of five months' duration. She had suffered from *angina pectoris* for three years and had had one definite attack of cardiac failure. She had been a diabetic under treatment for fourteen years. The classical features of untreated myxedema were present. No thyretoid gland was palpable. The extremities exhibited cardiac edema. The heart was moderately enlarged. The systolic blood pressure was 145 and the diastolic pressure 105 millimetres of mercury. Her urine, on her admission to hospital, was acid; the specific gravity was 1.010; a large amount of sugar and some acetone were present.

On investigation the red cells were found to number 4,010,000 per cubic millimetre and the hæmoglobin value was 88%. The sugar tolerance was greatly diminished. X-ray examination of the chest revealed some cardiac hypertrophy. The pituitary fossa was normal. The electrocardiogram revealed a low voltage curve in all leads with a flattened T wave. The initial mean basal metabolic rate was -30%, and the blood cholesterol content was 369 milligrammes per centum. The diabetes and cardiac failure were controlled by appropriate measures.

After stabilization of the basal metabolic rate and the blood cholesterol value, venesection was performed to allow the patient's blood to be tested for thyretrophic and antithyretrophic factors. Seven days later she received a test dose of sterilized thyretrophic hormone (100 units subcutaneously), and four days later a large single dose of 4,000 units of hormone. Blood samples were removed two and four hours after the injection for test purposes. The basal metabolic rate and blood cholesterol values were closely studied after the administration of hormone.

The results of this clinical and experimental investigation are shown in the appended graph (Figure I) and Tables I, III and IV. The basal metabolic rate and blood

cholesterol values showed no response to the injection of 4,000 units of thyretrophic hormone. The final, rather lower, cholesterol value shown was an isolated one, and was not repeated in subsequent evaluations made. Clinically, the pulse rate, body weight and subjective sense of well-being were unchanged. In contrast, subsequent administration of 10 milligrammes of pure crystalline thyroxine in alkaline solution by mouth caused a prompt rise in metabolic rate, a fall in blood cholesterol level, pronounced acceleration of the pulse rate, a loss of six pounds in body weight, nervousness, sweating, palpitation and pronounced weakness.

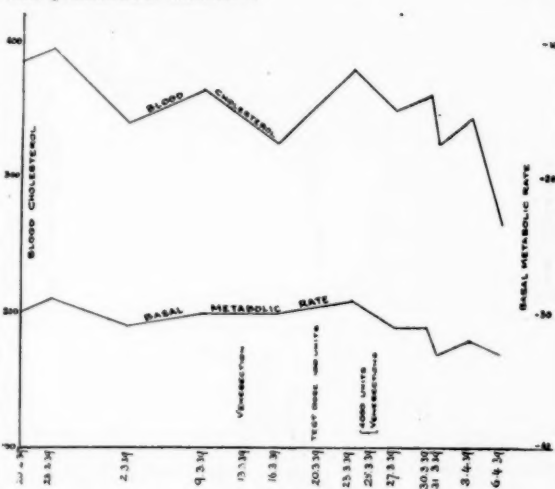


FIGURE I.

Evaluation of the antithyretrophic factor gave negative results.

The results show quite clearly that no evidence of thyretrophic or antithyretrophic factors could be found in the blood of this patient. No thyretrophic hormone could be recovered from the blood immediately after the administration of a large dose of the hormone to the patient.

CASE II.—Mrs. M.M., aged sixty-six years, had noticed a lump in her neck for three and a half months before coming to hospital, and had experienced dryness of the mouth and throat, sleeplessness and loss of appetite over a corresponding period. She had been nervous, excitable and unsteady in her movements for about one year. She had had no previous illnesses or operations, but had suffered severe mental stress as a result of family worries fifteen years earlier. She had been reared in and had been a resident of the New England district, New South Wales, until twenty-one years earlier, since when she had lived in Sydney.

On examination she presented an obvious nodular enlargement of the thyretoid gland, more noticeable on the left side. The skin was warm and moist, tremor was pronounced, and tachycardia was moderate (the pulse rate was 90 per minute). Eye signs were normal. The heart was of normal size; *pulsus alternans* was present. The systolic blood pressure

TABLE I.
Evaluation of Thyretrophic Factor.

Time of Sampling and Volume of Blood Extracted.	Guinea-pig Number.	Initial Weight. (Grammes.)	Final Weight. (Grammes.)	Period of Injection. (Days.)	Weight of Gland. (Milligrammes per 100 Grammes.)		Histology of Thyroids.
					Thyretoid.	Adrenals.	
Blood before injection, 112 cubic centimetres	T 125	208	172	5	9.2	84.3	Normal gland.
	T 127	212	208	5	13.8	60.0	Normal gland.
Blood two hours after injection, 100 cubic centimetres	T 136	179	192	4	8.9	90.6	Normal gland.
	T 141	202	148	4	12.7	92.7	Normal gland.
Blood four hours after injection, 100 cubic centimetres	T 138	170	204	4	10.8	61.3	Normal gland.
	T 135	174	169	4	10.6	94.6	Normal gland.

Evaluation of the antithyretrophic factor gave negative results.

was 160 and the diastolic pressure 90 millimetres of mercury. The other systems presented no abnormality. The urine contained no abnormal constituents. An electrocardiographic examination revealed extrasystoles.

The condition was presumably one of long-standing thyrotoxicosis, which had reached a phase of degeneration. The average basal metabolic rate after stabilization was +12%, and the blood cholesterol value was 128 milligrammes per centum.

Parallel observations to those in Case I were carried out for the detection of thyreotropic hormone, except that the dosage of thyreotropic hormone administered was 2,000 units. The results are shown in the graph (Figure II).

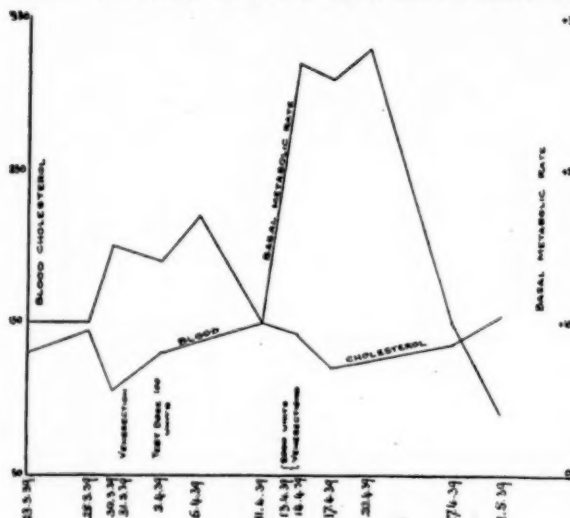


FIGURE II.

The basal metabolic rate rose to a maximum of +28% and returned to the pre-injection level within fourteen days of the injection of thyreotropic hormone. The blood cholesterol values underwent no significant variation over the corresponding period. Increased tachycardia, palpitation, restlessness, pallor and sweating were present for several days after the injection.

Samples of urine voided two and four hours after the injection were examined by an identical technique with negative result.

Evaluation of antithyreotropic factor gave negative results.

The results in this case therefore also failed to reveal the presence of either thyreotropic or antithyreotropic factor in the blood. No thyreotropic activity could be demonstrated in the blood or urine soon after the administration of a single large intramuscular injection of thyreotropic hormone to the patient.

CASE III.—Mrs. C.T., aged fifty years, presented an example of severe Graves's disease. For two years she had experienced dryness of the mouth and throat, a smothering feeling in

the chest, trembling, excessive perspiration, palpitation, and attacks of vomiting preceded by severe headache. She had been losing weight for six months, more rapidly in the past two months. She had undergone a panhysterectomy ten years previously, for a growth the nature of which could not be ascertained. She was a resident of Sydney, and one daughter had undergone thyroidectomy twelve months earlier.

On examination she appeared to be an extremely nervous and excitable woman. Pronounced tremor was present, exophthalmos was obvious, the skin was warm and moist. The thyroid gland exhibited a moderate uniform enlargement. Tachycardia was present. The eye signs were indicative of thyroid disease. Examination of the respiratory and alimentary systems revealed no abnormality, and the urine contained no abnormal constituents. The electrocardiogram revealed no abnormality.

After stabilization under the hospital régime the basal metabolic rate (the average of three determinations) was +37% and the blood cholesterol value was 131 milligrammes per centum. Venesection was performed at this juncture, and evaluations of the thyreotropic and antithyreotropic content were carried out. No evidence of the presence of either activity could be found.

CASE IV.—Mrs. M.W., aged fifty-two years, had had symptoms of hyperthyroidism for eight months. For this time she had experienced weakness, lassitude and tremor, hyperhidrosis, intolerance of hot weather, increased appetite and constipation. Palpitation and slight breathlessness on exertion were occasionally present. She had noticed temporary blurring of vision and diplopia six months earlier. She had lost three stone in weight during the past three years. The menopause had occurred twelve months earlier. All her seven children were alive and well, and there was no history of any gynecological disorder. She had been a Sydney resident for twenty years, having previously lived at Goulburn, New South Wales.

On examination she appeared flushed, excitable and nervous. The skin was hot and sweating; tremor was obvious in every movement. The thyroid gland presented a slightly irregular adenomatous enlargement, more pronounced on the right side. A systolic thrill and murmur were present over the gland. Exophthalmos and eye signs were absent. Tachycardia was pronounced; the heart was not enlarged, but a soft systolic murmur was audible just inside the apex beat. Other systems presented no abnormality.

The patient was placed under standard conditions in hospital, and exhibited a steady basal metabolic rate (average of three determinations) of +50%, the corresponding average cholesterol value being 123 milligrammes per centum.

Evaluations of thyreotropic and antithyreotropic factors were then made as before. No evidence of the presence of either could be found. The patient's metabolic rate exhibited a spontaneous fall to a level of +39% after the venesection, the lowest single reading previously recorded being +47%.

CASE V.—Miss D.M., aged twenty-five years, was also suffering from Graves's disease. For two years she had suffered from severe frontal headache and from severe stabbing pain in the lumbar region accompanied by a feeling of weakness. During this period she had lost a stone in weight. For the past four months she had noticed sweating, palpitation, nervousness, trembling and excitability. A lump developed in the neck. Menstruation had been very irregular since the menarche, the patient often having intervals of four to nine months between menses. Whooping cough had been the only previous malady. The patient was born in Coonamble, New South Wales, and had lived in Sydney since the age of nine years.

TABLE II.
Evaluation of Thyreotropic Factor.

Time of Sampling and Volume of Blood Taken.	Guinea-pig Number.	Initial Weight. (Grammes.)	Final Weight. (Grammes.)	Period of Injections. (Days.)	Weight of Glands. (Milligrammes per 100 Grammes.)		Histology of Thyroids.
					Thyroid.	Adrenals.	
Blood before injection, 100 cubic centimetres	T 164	158	166	4	8.4	73.2	Normal gland.
	T 160	178	165	4	9.0	69.6	Normal gland.
Blood two hours after injection, 100 cubic centimetres	T 181	206	208	4	10.1	45.6	Normal gland.
	T 184	191	156	4	7.3	106.7	Normal gland.
Blood four hours after injection, 100 cubic centimetres	T 182	200	204	4	8.3	—	Normal gland.
	T 183	178	180	4	10.0	55.6	Normal gland.

On examination the patient appeared nervous, irritable and excitable. The skin was warm and moist; tremor was gross and coarse. The thyroid gland presented an easily visible soft, diffuse, symmetrical enlargement. Pulsation could be felt over the gland, and a murmur was heard on auscultation over the surface. Exophthalmos was not very pronounced and eye signs were indefinite. Tachycardia was present; the pulse rate was 130 per minute. The apex beat was of large amplitude and had a slapping character; but there was no cardiac enlargement, and no murmurs were present.

After stabilization the basal metabolic rate (average of four determinations) was +21% and the blood cholesterol level was 143 milligrammes *per centum*. Examination of the blood for the presence of thyretrophic hormone gave negative results; examination for antithyretrophic factor gave positive results.

CASE VI.—Miss R.B., aged twenty-seven years, suffered from primary hypopituitarism and secondary hypothyroidism. Three years earlier the menses had ceased for six months and the patient's weight had increased from eleven to fourteen stone. The menses returned temporarily for eleven months, the body weight during this period again falling to eleven stone. Since then the menses had become increasingly scanty, finally disappearing eleven months before her admission to hospital. The patient had since suffered from vertigo, violent frontal headache, vomiting and numbness of the extremities. She had flashes of light before the eyes, with intermittent blurring of vision. The appetite was capricious; pain in the epigastric region was sometimes noticed. The present weight was fifteen stone. The patient's intelligence and memory were stated to be unaffected.

On examination she presented the picture of gross obesity of pituitary type. The hair and nails appeared normal, the eyebrows were scanty, the extremities were tapered and felt cold and clammy. The thyroid gland was not palpable. Apart from exaggerated reflexes, no abnormality could be detected in the nervous system. The circulatory, respiratory and alimentary systems presented no abnormality. The urine was acid and contained no abnormal constituents.

On investigation doubtful temporal pallor was observed in the ocular fundi. The visual fields exhibited a concentric peripheral contraction. Pressure of cerebro-spinal fluid was 200 millimetres; Queckenstedt's test gave a positive result, and the fluid contained no abnormal constituents. The Wassermann test produced no reaction in either blood or cerebro-spinal fluid. The sugar tolerance was normal, and no abnormality was observed in the pituitary fossa. The basal metabolic rate three months before the patient's admission to hospital was found to be -28%, and thyroid medication had been instituted but discontinued three weeks before her admission.

After stabilization the mean basal metabolic rate was still +7% and the mean blood cholesterol value was 149 milligrammes *per centum*. After venesection the patient was given on two successive days intramuscular injections, each of 1,000 units of thyretrophic hormone. She experienced a severe reaction to the hormone within eighteen hours of the first injection, with nausea, vomiting, profuse perspiration, tachycardia and an obvious tender swelling of the thyroid gland. Simultaneously she experienced quite pronounced abdominal and sacral pain resembling the former menstrual pain; but no menstruation actually occurred.

Determinations of the basal metabolic rate and the cholesterol value were made to enable the response to the injections to be followed. The basal metabolic rate rose to a maximum value of +31%, and the blood cholesterol values remained unchanged. The marked clinical and metabolic response confirmed the diagnosis and the ability of the thyroid gland to react to its physiological stimulus. The examination of the blood for thyretrophic and antithyretrophic factors gave negative results.

CASE VII.—Miss G.M. was suffering from Graves's disease and had a basal metabolic rate within normal limits. She had a history of breathlessness, palpitation, trembling and loss of weight of two stone over a period of four months. She also complained of lumbar pain, weakness of the arms and legs, nervousness, irritability and sweating. Previous illnesses included scarlet fever, measles and whooping cough. Two relatives suffered from exophthalmic goitre. She had been born in northern New South Wales, but had lived in Sydney for eighteen years.

On examination she was a restless excitable girl, exhibiting slight exophthalmos. Her skin was warm but not moist. There was a diffuse symmetrical enlargement of the thyroid gland, and a systolic murmur was audible on auscultation over the gland. The eye signs were indicative of thyroid disease. Tremor affected the right hand only. The pulse rate was very rapid (140 per minute) and regular; the systolic blood pressure was 150 and the diastolic pressure 110 millimetres of mercury. The heart was not enlarged

and presented no abnormality apart from tachycardia. Other systems were normal. The urine was acid; it contained no abnormal constituents.

As an out-patient four months earlier the patient had had a basal metabolic rate of +18%. Prior to this she had had a course of iodine therapy for six weeks. The electrocardiogram revealed sinus tachycardia and doubtful signs of a former posterior coronary infarction in Lead III. The stabilized basal metabolic rate was +4%, and the blood cholesterol value was 160 milligrammes *per centum*.

Evaluations of thyretrophic and antithyretrophic factors in the blood were performed. No thyretrophic hormone was found, but antithyretrophic factor was present.

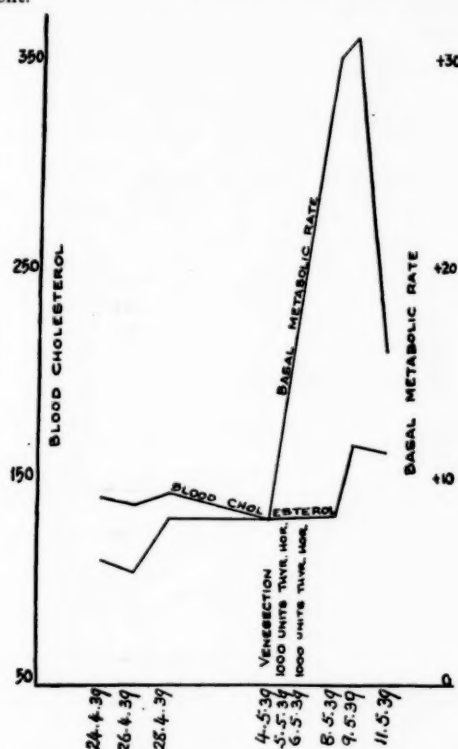


FIGURE III.

The detailed and summarized results of the investigation of thyretrophic and antithyretrophic factors are shown in Tables III and IV.

Discussion.

The investigations carried out in this paper, though of necessity restricted to a small number of cases, have nevertheless included types of the four major disorders of the thyroid gland. The results are consistent with the following interpretations.

No thyretrophic hormone is demonstrable in the blood of patients suffering from hyperthyroidism, whether of so-called primary or secondary origin, even when a reliable concentration process is used to extract relatively large quantities of the blood to be tested. The findings of Fellingner⁽⁶⁾ cannot be confirmed; but the results are in harmony with those of Cope, and Hertz and Ostler.⁽⁸⁾ It would appear, too, that no thyretrophic hormone is recoverable from the blood of patients with spontaneous myxedema, as already found by Cope and by Spence.⁽¹⁰⁾ Hertz and Ostler, however, found large quantities of thyretrophic hormone in the blood and urine of patients rendered myxedematous after complete thyroidectomy. The fact that these cases may fall into a different category from those of spontaneous myxedema has already been discussed by Cope.

TABLE III.
Evaluation of Thyreotropic Hormone in Blood.

Case Number.	Diagnosis.	Basal Metabolic Rate per Centum.	Blood Cholesterol Content. (Milligrammes per Centum.)	Volume of Blood Withdrawn. (Cubic Centimetres.)	Period of Injection. (Days.)	Weight of Thyroid. (Milligrammes per 100 Grammes Body Weight.)	Number of Test Animal.	Result of Evaluation.
I	Myxœdema, diabetes mellitus	-30	383	112	5	9.2	T 125	} Negative.
		-29 -30	393 369		5	13.8	T 127	
		-31	342					
		-30	356					
II	Toxic adenoma	+10	130	100	4	8.4	T 164	} Negative
		+10 +12	145 128		4	9.0	T 160	
		+15	106					
III	Graves's disease	+37	138	100	4	9.6	T 163	} Negative
		+36 +37	117 131		4	13.4	T 162	
		+38	138					
IV	Toxic adenoma	+52	106	103	5	9.5	T 131	} Negative
		+51 +50	130 123		5	13.3	T 128	
		+47	133					
V	Graves's disease	+22	150	103	5	10.8	T 130	} Negative.
		+24 +21	134 143		5	14.6	T 129	
		+19	148					
		+18	138					
VI	Hypopituitarism. Secondary hypothyroidism	+6	163	100	4	15.0	T 201	} Negative.
		+5 +7	140 149		4	14.1	T 199	
		+8	143					
VII	Graves's disease	+5	154	100	4	11.0	T 202	} Negative.
		+3 +4	166 160		4	10.6	T 200	
Control experiments.	50 units thyroid hormone added			112	4	15.0 12.4	T 115 + + T 117 +	} Positive.

TABLE IV.
Evaluation of Antithyreotropic Factor in Blood.

Case Number.	Nature of Injection.		Period of Injection. (Days.)	Weight of Thyroid. (Milligrammes per 100 Grammes.)	Number of Test Animal.	Histology of Thyroid.	Result of Evaluation.
	Total Blood Injected. (Cubic centimetres.)	Amount of Thyroid Hormone Injected. (Units in 1 part.)					
I	12	2 x 2½	6	11.9	T 145	+	Negative.
	12	2 x 5	6	14.4	T 142	++	
	12	2 x 5	6	8.5	T 147	-	
II	12	2 x 2½	6	13.8	T 153	+	Negative.
	12	2 x 5	6	14.3	T 149	++	
	12	2 x 5	6	11.4	T 151	++	
III	12	2 x 2½	6	13.4	T 150	+	Negative.
	12	2 x 5	6	13.2	T 154	++	
IV	12	2 x 2½	6	10.9	T 146	+	Negative.
	11	2 x 5	6	11.6	T 144	++	
V	12	2 x 2½	6	10.0	T 133	-	Positive.
	12	2 x 2½	6	10.4	T 132	-	
VI	12	2 x 2½	6	16.6	T 195	+	Negative.
	12	2 x 5	6	10.5	T 197	++	
	12	2 x 5	6	16.2	T 196	++	
VII	12	2 x 2½	6	8.9	T 194	-	Positive.
	12	2 x 5	6	17.7	T 198	+	
Control experiments ..	12	2 x 2½	2	9.7	T 143	+	
		2 x 5		17.2	T 148	++	

It is doubtful, however, whether failure to demonstrate thyreotropic hormone in the blood of thyreotoxic patients invalidates the theory that the thyreotoxic state is attributable to an increased production of thyreotropic hormone by the anterior pituitary. In the first place, the excess production would have to be large indeed to produce in the blood a recognizable titre of a hormone which is readily diffusible and recoverable from tissue fluids only with difficulty. Secondly, excess hormone produced may be rapidly fixed or destroyed by the general body tissues, and it has been shown that some of it is excreted through the kidney (Loeser). The thyroid gland itself may differ-

entially adsorb circulating thyreotropic hormone which, though undemonstrable, is still able to exert its stimulating effect on the thyroid gland.

The difficulties inherent in demonstrating the presence of circulating thyreotropic hormone in humans are well illustrated by the two experiments reported here of the injection of large single doses of hormone into patients. The hormone preparation used was of standard potency, and its absorption into the general circulation and efficacy are proved from Figures II and III, depicting the rises in basal metabolic rate after its administration; but despite this, it was still impossible to recover thyreotropic sub-

stance from the blood after the administration of as large a dose of hormone as conveniently possible in two cases. The results afford definite proof that thyreotropic hormone in the human economy may give rise to pronounced clinical effects without being recoverable from the circulating blood.

Another possibility is that circulating thyreotropic hormone may be rendered unrecognizable by bioassay, owing to the concurrent presence of neutralizing substances in the blood, which protect the test animals' thyroid gland from the customary effect of the thyreotropic hormone. The occurrence, development and properties of such neutralizing antithyreotropic substances have been reviewed by Lambie.⁽¹⁰⁾

The possibility of their complicating the results of the present experiments has been investigated as far as possible by examination of the specimens of blood tested for their presence. However, in but two of the thyreotoxic patients and in none of those with hypothyroidism could a positive antithyreotropic activity of the blood be detected. It is not intended to draw conclusions from such scanty findings; but the results do lend support to the theory that antithyreotropic substances present in blood may contribute in some part to the complex and often conflicting symptomatology in the various types of thyroid diseases; and it is interesting to observe that these antithyreotropic substances were detected in the blood of the only two young patients investigated, one of whom had already received, in addition, a course of iodine therapy. The failure to detect antithyreotropic substances in the remaining cases does not, however, eliminate the possibility of their presence in those cases. It is quite conceivable, as suggested by Trikojus,⁽¹²⁾ that even normal blood contains both thyreotropic and antithyreotropic substances existing in a balanced state, which preserves the functional activity of the thyroid gland within normal limits. In the various types of thyroid disease this balance may be upset or altered in a variety of ways, which produce the several types of thyroid disorders. The problem must remain unsolved, however, pending further investigations of the production, nature and distribution of these ill-understood protective substances.

As regards the cholesterol evaluations made in this paper, it is interesting to note that in the case of myxœdema, both basal metabolic rate and blood cholesterol value alike were uninfluenced by the administration of thyreotropic hormone. Two cases of myxœdema were investigated by Harrison;⁽⁷⁾ in the operative case there was no alteration, and in the spontaneous case only a slight fall in the level of blood cholesterol. The present case was admittedly complicated by *diabetes mellitus*; but the combined results would appear to show that there exists a fairly close relationship between the basal metabolic rate and the blood cholesterol level when raised, in regard to their sensitivity to the thyreotropic hormone. This would support the evidence of Schnitker, Raalte and Cutler⁽¹³⁾ in deducing the dependence of the blood cholesterol level on the presence or absence of thyroid tissue, and the influence of the thyreotropic hormone on it only through the mediation of thyroid tissue. On the other hand, animal experiments performed in this department (to be published elsewhere) seem to indicate that the thyreotropic hormone is able to influence directly the blood cholesterol level in rabbits rendered hypercholesterolaemic by prolonged feeding with cholesterol, without the mediation of the thyroid gland.

Summary.

A reliable method for the concentration and extraction of thyreotropic hormone from whole human blood has been described. The blood of seven patients suffering from four types of thyroid disease has been tested for the presence of thyreotropic hormone by this method, with negative results in every case. In two cases it was not possible to detect any thyreotropic hormone in blood removed very shortly after the intramuscular injection of a large single dose of thyreotropic hormone, although clinical evidence of the absorption and physiological action of the hormone was present.

The blood of each patient has also been examined for the presence of protective antithyreotropic substances, with positive results in two cases. The significance and interpretation of these findings have been discussed.

Determinations of the basal metabolic rate and the blood cholesterol level have been performed in each case. The results have been discussed in relation to the similar series recently published from this department.

It is concluded that thyreotropic hormone cannot be detected in the blood of patients suffering from the types of thyroid disorders investigated, but that this fact does not invalidate the theory that alterations in the rate of production and discharge of the thyreotropic hormone of the anterior pituitary may be primarily responsible for many types of thyroid disease.

Acknowledgements.

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References.

- (1) J. B. Collip and E. M. Anderson: "Production of Serum Inhibitory to Thyrotropic Hormone", *The Lancet*, Volume I, 1934, page 76.
- (2) J. B. Collip and E. M. Anderson: "Preparation and Properties of Antithyrotropic Substance", *The Lancet*, Volume I, 1934, page 784.
- (3) C. L. Cope: "The Anterior Pituitary Lobe in Graves' Disease and in Myxœdema", *The Quarterly Journal of Medicine*, Volume VII, 1938, page 151.
- (4) A. Crotti: "Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter", 1938, page 258.
- (5) H. Eitel, H. A. Krebs and A. Loeser: "Die Wirkung der thyreotropen Substanz des Hypophysenvorderlappens auf die Schilddrüse in vitro", *Klinische Wochenschrift*, Volume XII, 1933, page 615.
- (6) K. Fellinger: "Über das Verhalten und die Bedeutung des thyreotropen Hormons", *Münchener medizinische Wochenschrift*, Volume LXXXIII, 1936, page 1115.
- (7) K. S. Harrison: "Clinical Application of Thyreotropic Hormone", *THE MEDICAL JOURNAL OF AUSTRALIA*, Volume I, 1939, page 681.
- (8) S. Hertz and E. G. Oastler: "Assay of Blood and Urine for Thyreotropic Hormone in Thyreotoxicosis and Myxœdema", *Endocrinology*, Volume XX, 1936, page 520.
- (9) C. G. Lambie: "The Thyreotropic Hormone and its Relation to Clinical Syndromes", *THE MEDICAL JOURNAL OF AUSTRALIA*, Volume II, 1939, pages 819 and 853.
- (10) L. Loeb and R. B. Bassett: "Comparison of Effects of Various Preparations of Anterior Pituitary Gland on Thyroid of the Guinea Pig", *Proceedings of the Society for Experimental Biology and Medicine*, Volume XXVII, 1930, page 490.
- (11) A. Loeser: "Die Schilddrüse wirksame Substanz des Hypophysenvorderlappens", *Archiv für experimentelle Pathologie und Pharmakologie*, Volume CLXXVI, 1934, page 697.
- (12) R. Müller, H. Eitel and A. Loeser: "Der thyreotrope Wirkstoffgehalt der menschlichen Hypophyse", *Archiv für experimentelle Pathologie und Pharmakologie*, Volume CLXXIX, 1935, page 427.
- (13) M. T. Schnitker, L. H. Raalte and E. C. Cutler: "Effect of Total Thyroidectomy in Man: Laboratory Studies and Observations of Clinical Effects in 39 Cases", *Archives of Internal Medicine*, Volume LVII, 1936, page 857.
- (14) A. W. Spence: *The British Medical Journal*, Volume I, 1937, page 1277.
- (15) A. W. Spence and L. J. Witts: "Substitution Therapy in Hypopituitarism", *The Quarterly Journal of Medicine*, New Series, Volume VIII, 1939, page 69.
- (16) W. O. Thompson et alii: "Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter", 1938, page 250.
- (17) K. W. Thompson: "Transactions of the Third International Goiter Conference and the American Association for the Study of Goiter", page 256.
- (18) V. M. Trikojus: "The Role of Iodine (KI) in Experimental Hyperthyroidism", *THE MEDICAL JOURNAL OF AUSTRALIA*, Volume I, 1939, page 220.

AN INVESTIGATION INTO THE TYPE INCIDENCE OF PNEUMOCOCCI IN INFECTIONS OF THE LOWER RESPIRATORY TRACT.¹

By ELIZABETH A. STORO and E. MARJORY LITTLE.
(From the Kanematsu Memorial Institute of Pathology, Sydney Hospital, Sydney.)

THIS investigation into the type incidence of pneumococci in infections of the lower respiratory tract was commenced in June, 1938. At that time chemotherapy had not replaced serum therapy in the treatment of lobar pneumonia, and it was hoped that, by discovering the prevailing local types, the importation or manufacture of homologous therapeutic and diagnostic serum could be placed on a rational basis. When the efficacy of sulphapyridine in pneumococcal infections was finally established in 1939 the ultimate object of the investigation was removed; but it was decided to continue as planned, partly because the only Australian figures concerning adults we were able to find were two small series presented by Dr. A. H. Tebbutt, of Sydney,⁽¹⁾ and by Dr. S. W. Patterson and Miss F. E. Williams, of Melbourne,⁽²⁾ at the Australasian Medical Congress in 1920 (Table I); and also

¹This investigation was carried out with the assistance of a grant from the National Health and Medical Research Council under the supervision of Dr. H. K. Ward, Professor of Bacteriology, University of Sydney.

because we agree with Cooper and her colleagues,⁽³⁾ who made the following suggestion.

Although there is no immediate benefit to individual patients in determining the type where no therapeutic serum is available it seems worth while to continue examination for all types and maintain a full supply of diagnostic antisera until it is learned whether there is a seasonal and periodical variation in the types in a locality and what their distribution in other localities is.

A request was made through THE MEDICAL JOURNAL OF AUSTRALIA and the monthly circular to members of the New South Wales Branch of the British Medical Association for specimens of sputum from patients suffering from infections of the lower respiratory tract, and during the 23 months over which the investigation extended (June 8, 1938, to April 30, 1940) we examined, after the rejection of those that appeared to consist of saliva only, 1,000 specimens of sputum. Of these, 850 were received from 17 hospitals in Sydney and its suburbs, 105 from doctors practising in the same area and 45 from doctors in country districts of New South Wales and southern Queensland. The survey is thus representative of the metropolitan district rather than of the State of New South Wales.

If pneumococci were present in large numbers an attempt was made to identify the type by Neufeld's *Quellung* reaction applied directly to the sputum. More often, however, a small portion of the sputum was emulsified in normal saline solution and one or two cubic

TABLE I.
Incidence of Pneumococcal Types in Australia Recorded by Other Observers.¹

Observers.	Period.	Number of Strains	Type I.	Type II.	Type III.	Group IV.	Doubtful.
A. H. Tebbutt	1919 and 1920	54	3	0	11	30	10
S. W. Patterson and F. E. Williams	1919	96	34	6	4	4	—

¹ These investigations were made before the pneumococci in Group IV were subdivided by Cooper and her colleagues into types.

TABLE II.

Type.	Number Recovered.	Percentage of Total Recovered.	Order of Frequency.	Lobar Pneumonia.		Lobular Pneumonia.	
				Cases.	Deaths.	Cases.	Deaths.
I	139	18.0	1	109	21	20	6
II	5	Less than 1	—	2	—	—	—
III	69	9.0	4	47	12	12	3
IV	56	7.0	5	40	9	9	1
V	51	7.0	6	45	4	1	—
VI	22	3.0	—	13	1	4	—
VII	82	10.0	3	48	2	20	9
VIII	101	13.0	2	71	10	16	3
IX	15	2.0	—	7	—	4	—
X	19	2.5	—	8	2	3	2
XI	5	Less than 1	—	4	—	7	—
XII	28	3.7	—	18	—	6	—
XIII	22	3.0	—	13	—	4	1
XIV	8	1.0	—	7	1	1	—
XV	14	1.8	—	10	3	3	2
XVI	5	Less than 1	—	4	2	—	—
XVII	11	1.4	—	7	2	2	—
XVIII	9	1.0	—	5	1	2	—
XIX	7	Less than 1	—	5	2	1	1
XX	29	3.8	—	18	1	6	—
XXI	7	Less than 1	—	1	—	5	3
XXII	18	2.5	—	8	1	4	—
XXIII	3	Less than 1	—	2	—	—	—
XXIV	1	Less than 1	—	—	—	—	—
XXV	—	—	—	—	—	—	—
XXVII	2	Less than 1	—	1	—	1	—
XXVIII	6	Less than 1	—	5	—	1	1
XXIX	2	Less than 1	—	2	1	1	—
XXXI	6	Less than 1	—	—	—	4	1
XXXII	4	Less than 1	—	3	—	—	—
Untyped	8	—	—	4	—	1	—
Total	754	—	—	507 ¹	70	138 ¹	33
No pneumococci recovered	—	—	—	104	15	60	3
Total	—	—	—	611	85	198	36

¹ The sum of these two figures is less than the total number of pneumococci recovered, as the attending doctors were not prepared to classify the pneumonia in 109 instances.

centimetres of the emulsion were injected into the peritoneal cavity of a mouse; when the mouse died or was killed an attempt was made to identify by direct typing the type of pneumococcus in the peritoneal exudate. A sample of heart blood was also incubated on blood agar, and after twelve to eighteen hours a colony was subcultured in glucose-serum-broth, and typing was carried out after six to eight hours' growth. Anti-pneumococcal serum for Types I, II and III were obtained from the Commonwealth Serum Laboratories and that for the other types was manufactured by and imported through Parke, Davis and Company.

Pneumococci were recovered in 754 of the 1,000 specimens of sputum included in the survey and the type incidence of the strains is presented in Table II. It will be noted: (i) that Types I, VIII, VII, III, IV and V in the order named were most frequently represented and accounted together for 66% of all pneumococci recovered; (ii) that all Cooper's types are represented except Type XXV, and (iii) that Type II was recovered in less than 1% of all specimens of sputum yielding pneumococci. The low incidence of Type II in this series is in striking contrast with the results of other investigators. Alston and Stewart⁽¹⁾ in an analysis of the records of fifteen groups of investigators in different parts of the world for the period 1913-1924, noted that Types I and II accounted for about 58% of all cases of pneumonia. It is interesting, however, to observe that Dr. Tebbutt in 1919 and 1920 failed to find a representative of Type II in the 54 strains he isolated in Sydney.

Doctors who sent specimens of sputum were asked to state their opinion as to the variety of pneumonia (lobar or lobular) from which the patient was suffering, and with this information an attempt was made to correlate the variety of pneumonia, the mortality rate and the type of infecting pneumococcus. Clinical notes were available for 929 specimens of sputum out of the 1,000 examined, and the attending doctors were prepared to state whether the pneumonia was of the lobar or lobular variety in 809 instances. The results of this analysis, which cannot be regarded as highly accurate, are incorporated in Table II.

The information supplied by practitioners also allowed us to form some idea of complications associated with the various types of pneumococci, and these are set out in Table III.

TABLE III.

Type of Pneumococcus.	Empyema.	Otitis Media.	Meningitis.	Pulmonary Abscess.	Pericarditis.
I ..	14 (2D) ¹	Lobar Pneumonia. 4 1 (D with empyema).	1 (D)	1 (D)	1 (D)
III ..	5 (2D)				
IV ..	2				
V ..	10 (1D)				
VI ..	2				
VII ..	4	2 (1D) 1 (D with empyema) 1 (D)	1 (D)	1 (D)	1 (D)
VIII ..	8 (2D)				
Other types	12 (3D)				
Total ..	55 (10D)	5	5 (4D)	1 (D)	8 (6D)
I ..	1	Lobular Pneumonia. 1 1	1	1	1 (D)
III ..	1				
IV ..	1				
Other types	1	1	1	1	1 (D)
Total ..	2	2	1	1	1 (D)

¹ "D" signifies "died".

The several instances in which two members of a family suffered from pneumonia simultaneously or in quick succession are recorded in Table IV.

TABLE IV.

Relationship between Patients.	Type of Pneumococcus Recovered from Sputum.	Result.
Father	VIII	Cured
Son	VIII	Cured
Husband	III	Died
Wife	III and VIII	Died
Wife	I	Cured
Husband	IV	Died
Daughter	X	Cured
Father	X and XX	Died
Wife	III	Empyema, cured
Husband	III	Cured

Summary.

1. The results of an investigation into the type incidence of pneumococci in infections of the lower respiratory tract in New South Wales are presented.

2. Specimens of sputum from 1,000 patients yielded pneumococci in 754 instances (75.4%).

3. Types I, VIII, VII, III, IV and V in the order named were most frequently represented and accounted for 66% of all pneumococci. Type II was recovered in less than 1%.

References.

- ⁽¹⁾ A. H. Tebbutt: "Transactions of the Eleventh Session Australasian Medical Congress", 1920.
- ⁽²⁾ S. W. Patterson and F. E. Williams: "Transactions of the Eleventh Session Australasian Medical Congress", 1920.
- ⁽³⁾ G. Cooper, C. Rosenstein, A. Walter and L. Pelzer: "Further Separation of Types among Pneumococci Hitherto Included in Group IV and Development of Therapeutic Antisera for These Types", *The Journal of Experimental Medicine*, Volume LV, April, 1932, page 531.
- ⁽⁴⁾ J. M. Alston and D. Stewart: "Incidence of Serological Types of Pneumococcus in Lobar Pneumonia", *The British Medical Journal*, Volume II, November 22, 1930, page 860.

AN OUTBREAK OF INFECTION DUE TO STREPTOBACILLUS MONILIFORMIS AMONG WILD MICE.

By STEPHEN WILLIAMS.

(From the Commonwealth Serum Laboratories, Parkville.)

In recent years, several outbreaks of an epizootic disease in mice due to the organism *Streptobacillus moniliformis* have been reported. Levaditi (1932), Mackie, Van Rooyen, and Gilroy (1933), and Strangeways (1933) have all reported its occurrence in stocks of laboratory mice. The disease described by these workers was characterized by septicaemia and multiple arthritis, and in its acute form was attended by a high mortality. Their investigations have clearly shown the *Streptobacillus moniliformis* to be the causal agent. Clinical interest in this organism has been aroused by its isolation from a number of human cases of rat-bite fever, and from the extensive "Haverhill fever" epidemic in America in 1926. From the bacteriological point of view, the observations of Klieneberger (1935) that a filtrable organism resembling that of pleuro-pneumonia occurred symbiotically with the streptobacillus have attracted considerable attention.

The present outbreak occurred amongst the wild mice (*Mus musculus*) in New South Wales, where it was first observed by farmers in June, 1940. During the previous summer the mice in a relatively small, well-defined area had multiplied to an abnormal extent, and in the autumn had reached plague proportions. With the onset of winter they were driven from the fields into wheat-stacks and houses, and there was thus an unusual opportunity for

observation of large numbers at close quarters. According to the local farmers, about 1% of mice were affected with the disease, although in one isolated wheat-stack as many as 90% were said to have shown lesions. As far as could be determined, there was no great mortality, nor any evidence that the disease caused a reduction of numbers. A comprehensive survey of the mouse population in the affected districts was not possible; but it appeared unlikely that the epizootic had a wide distribution, or that it existed in a form other than a chronic arthritic condition.

Nature of the Disease.

In all, some thirty mice from the areas involved were examined; the majority showed specific joint lesions. Their general condition was poor, while many showed evidence of wasting. Apart from the actual deformity resulting from the arthritis, their activity was not greatly impaired. They readily became adapted to laboratory conditions and remained under observation for many weeks. The joints most commonly involved were the wrist, ankle and tail vertebrae, the lesions appearing as bulbous fusiform swellings affecting the whole joint. Incision into swellings disclosed a quantity of thick caseous material, with considerable disorganization of the joint structures. The tail lesions, which consisted of one or more swellings along its length, were sometimes associated with scarred depressions, suggesting older healed lesions. A number of mice showed simultaneous involvement of two or more joints.

Post-mortem examination revealed enlargement of the regional and abdominal lymph nodes and a moderate enlargement of the spleen. Occasionally, small abscesses were found in the spleen. No abnormality was detected in the heart, lungs and remaining abdominal viscera.

The disease was essentially chronic in nature. Observations of the progress of the wild mice in the laboratory revealed a tendency to spontaneous recovery, with the disappearance of the joint swellings. A number died of intercurrent infection, and several deaths were attributed to a widespread skin infection of *Achorion quinckeanum*, the so-called "mouse favus" fungus. This condition was coincidentally present in nearly all the mice, and caused deaths by spreading over the whole face. In no case could death be specifically ascribed to the presence of the streptobacillus. Of the mice originally showing lesions, some were alive at the end of four months and had shown a considerable degree of healing. In one case, however, a joint abscess remained chronically active for this period.

Bacteriological Findings.

Direct smears of the joint material showed disintegrating leucocytes and granular debris, amongst which were large numbers of slender bacilli varying in length from one to three μ . They were Gram-negative and were not acid-fast. On culture a plentiful growth of *Streptobacillus moniliformis* was obtained, appearing on solid media after two days at 37° C., as small transparent dew-drop colonies measuring 0.2 to 1.0 millimetre in diameter; in broth cultures a characteristic "bread-crumbs" growth occurred, consisting of large fluffy granules settling in the bottom of the tube. Of the ordinary laboratory media, blood agar and Loeffler slopes gave satisfactory results, but nutrient broth and agar required enrichment with sterile normal horse serum, no growth occurring without the addition of at least 10% of serum. Cultures remained viable for a short time only—usually five to seven days—and frequent subculturing was necessary to keep the strain alive. Although these observations were made under aerobic conditions, anaerobic cultures appeared to yield equally good results. The most striking feature of this organism was its remarkable pleomorphism on culture. The strain isolated in the present work corresponded closely to those described in the elaborate studies made by Klieneberger (1936) and Dienes (1939). By means of direct smear preparations stained with dilute basic fuchsin, it was possible to demonstrate the initial development of a twisted non-branching mycelial structure, its fragmentation into bacillary rods, the presence of deeply staining

fusiform swellings, and finally the degenerative changes reducing the colonies to structureless granular material. In contrast to the short bacillary forms seen in smears from lesions, many long filamentous threads reaching as much as 200 μ in length were found in the cultures.

A brief attempt to identify the "L.I." colonies of Klieneberger was made, without success. At no time, in primary cultures or in any of the numerous subcultures, was there evidence of a colony type other than that of the *Streptobacillus moniliformis* described. Filtration experiments were carried out with samples of pus and broth cultures, by means of Seitz "EK" filters. Numerous minute granular bodies were detected in the filtrates under dark-ground examination, but invariably they remained sterile. They were also non-pathogenic for mice, and produced no effect on developing eggs.

Pathogenicity.

Experimental inoculations were carried out on 58 laboratory mice. Although there was some individual variation of response, in general they showed a greater susceptibility to the streptobacillus than did the wild mice. A small amount (0.02 cubic centimetre) of pus or culture injected into a hind-foot pad led to an excellent reproduction of the disease. A local swelling was followed in two to four days by an involvement of the corresponding ankle joint. In the course of a further ten days the disease became generalized, with the appearance of other joint lesions, oedema of the feet and tail, and a purulent conjunctivitis which completely occluded the palpebral fissure. Death usually occurred within three or four weeks. The post-mortem findings were similar to those described in the wild mice, except that the lymph glands were more widely affected and often contained abscesses. Suppurative pericarditis was found in the hearts of several mice, while in two cases actual abscess formation of the heart wall was found. In all cases in which an attempt at culture from the blood was possible, either from very recently dead mice or from mice killed when moribund, the heart blood gave a positive result, indicating the septicæmic nature of the disease.

Intraperitoneal inoculation gave rise to substantially the same type of illness. Of sixteen mice inoculated by this route, only two showed the rapidly fatal septicæmic infection which was so frequently met with by Van Rooyen (1936) in his laboratory stock infections. The rest remained alive for ten to thirty days, ultimately dying after a more chronic course. At the post-mortem examination of these mice, an extraordinary degree of abscess formation in the abdominal cavity was found, the liver and spleen containing multiple large areas of caseation and the omentum showing numerous smaller suppurative lesions. In three cases a polyarthritis developed from intraperitoneal inoculation.

In view of Van Rooyen's observations that different strains of laboratory mice showed considerable variation in their susceptibility to experimental infections with this organism, a pure albino strain and a hybrid strain were both used in these investigations. Both strains showed approximately the same degree of susceptibility, developing, even with large doses of fresh cultures, a slowly progressive but ultimately fatal infection.

In order to estimate, in some measure, the possibility of transmission of the disease to human beings, a small number of examinations was made for the presence of the streptobacillus in the mouth and naso-pharynx of infected mice. Following the technique of Strangeways, who isolated similar organisms from the naso-pharynx of rats, five mice were examined at an advanced stage of the disease. Naso-pharyngeal swabs were inoculated into serum broth, and the resulting growth was inoculated into two further mice. In four of the five cases the organism was recovered in one or both of the test mice. It may be noted in this connexion that the writer and an assistant were bitten several times while handling infected wild mice, without any ill effect.

Guinea-pigs and rabbits were inoculated subcutaneously and intravenously with living cultures, but failed to show any evidence of the disease.

Discussion.

In assessing the significance of this outbreak of infection among wild mice, more particularly from the public health point of view, it is necessary to consider the question of similar infections in human beings. Parker and Hudson (1926) reported an extensive epidemic amongst the residents of Haverhill, Massachusetts, while some twenty sporadic cases have been recorded. In these last cases there was a more or less definite history of a rat bite preceding the illness. As the *Streptobacillus moniliformis* has been shown to be a normal inhabitant of the naso-pharynx of apparently healthy rats, the source of infection of these persons would seem to be obvious. The origin of the Haverhill epidemic is more obscure, and although a certain amount of evidence pointed to the milk supply, the conditions were such that direct murine contamination could not be excluded. Levaditi, citing the case of a laboratory worker who contracted the disease after handling white mice, has emphasized the possibility of infection from contamination of food by urine and faeces of diseased animals. He also considered this one of the chief means of natural transmission among mice, although direct proof is lacking on this point. Van Rooyen, on the other hand, quoting other workers, stated that the urine of infected mice was not infective for healthy animals. While admitting that no conclusions can be drawn regarding the natural mode of spread, he thinks that bites from diseased mice are partly responsible. Strangeways found no evidence that the streptobacillus occurred naturally in the naso-pharynx of healthy mice, but the positive findings in the small group of infected mice examined in this investigation suggest that, during the infective stage at least, transmission by bites is likely.

The virulence of mouse strains for human beings has not so far been established, Levaditi's case alone providing indirect evidence of transmission. If the type and severity of the disease produced experimentally in laboratory mice are taken as an index, strains from human and murine sources are of comparable virulence, while the strain isolated from the wild mice appears to be of a somewhat lower virulence.

Although there is a lack of detailed knowledge on these points, there can be no doubt of the association of human cases with a murine reservoir of infection, and it is therefore of some interest to record the disease in wild mice, in contrast with previous reports which have concerned laboratory stocks only. The special biological circumstances of the mouse population in which this outbreak appeared may well have played a part, possibly an essential one, in the development and spread of the infection. Such plagues of mice are by no means uncommon in Australia, and they necessarily bring about a degree of human contact which is not met with under normal conditions. It is suggested that the appearance of the disease in mice, combined with an abnormal increase in the mouse population, may have a potential importance with regard to the transmission of this infection to human beings.

Summary.

An outbreak of an infectious disease due to *Streptobacillus moniliformis* amongst wild mice in Australia is reported. The relationship of this occurrence to possible human infections is discussed.

Acknowledgements.

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Bibliography.

- L. Dienes: "L. Organisms of Kleneberger and Streptobacillus Moniliformis", *The Journal of Infectious Diseases*, Volume LXV, 1939, page 24.
 E. Kleneberger: "The Natural Occurrence of Pleuropneumonia-like Organisms in Apparent Symbiosis with Streptobacillus Moniliformis and Other Bacteria", *The Journal of Pathology and Bacteriology*, Volume XL, 1935, page 93.
 E. Kleneberger: "Further Studies on Streptobacillus Moniliformis and its Symbiont", *The Journal of Pathology and Bacteriology*, Volume XLII, 1936, page 587.
 C. Levaditi, R. F. Selbie and R. Schoen: "Le rhumatisme infectieux spontané de la souris, provoqué par le Streptobacillus moniliformis", *Annales de l'Institut Pasteur*, Volume XLVIII, 1932, page 308.
 T. J. Mackie, C. E. Van Rooyen and E. Gilroy: "An Epizootic Disease Occurring in a Breeding Stock of Mice: Bacteriology and Experimental Observations", *The British Journal of Experimental Pathology*, Volume XIV, 1933, page 132.
 F. Parker, Junior, and N. P. Hudson: "The Etiology of Haverhill Fever (Erythema Arthriticum Epidemicum)", *The American Journal of Pathology*, Volume II, 1926, page 357.
 W. I. Strangeways: "Rats as Carriers of Streptobacillus Moniliformis", *The Journal of Pathology and Bacteriology*, Volume XXXVII, 1933, page 45.
 C. E. Van Rooyen: "The Biology, Pathogenesis, and Classification of Streptobacillus Moniliformis", *The Journal of Pathology and Bacteriology*, Volume XLIII, 1936, page 455.

Reports of Cases.

A FATAL HUMAN INFECTION WITH STREPTOBACILLUS MONILIFORMIS.

By PHYLLIS M. ROUNTREE and M. ROHAN,
 Saint Vincent's Hospital, Melbourne.

THE following are the clinical history and bacteriological notes of a fatal infection with *Streptobacillus moniliformis* in a young girl.

Clinical Record.

Miss E.O.L., aged fourteen years, a resident of a suburb of Melbourne, was admitted to hospital on September 3, 1940, complaining of pain in the right side of the abdomen and in the right arm. Her mother stated that she had been told that, at the age of six years the child had a heart murmur, but the past history contained nothing else of significance until the onset of the present illness, which commenced about two months before the girl's admission to hospital with pain in the legs, side and back. About one month previous to her admission to hospital the patient had developed a severe sore throat associated with severe pain in the right side of the abdomen. This pain rapidly became generalized throughout the body and later began to affect mainly the joints and muscles of the limbs, particularly the muscles of the arm; the joints, however, did not become swollen. The sore throat cleared up in about a week; but about this time the patient developed a macular pinkish-red rash over the body and on the arms, which lasted only a few days. The pain, however, became progressively worse.

Examination on her admission to hospital revealed a well-grown and well-nourished girl with a greatly enlarged heart; the apex beat was six inches from the mid-sternal line in the fourth left intercostal space. There was a slapping first sound at the mitral area followed by a systolic murmur conducted into the axilla and up the left border of the sternum. The second sound was clear and no diastolic murmur was heard. No abnormality was detected in the aortic and pulmonary areas or in the lungs. Diffuse tenderness was present over the whole of the abdominal wall, but no mass or enlarged viscus was palpable. There was no joint or muscle tenderness in the left arm, left leg or right leg, but the right arm was exceedingly painful on movement at the shoulder joint, and there was a reddened hot area down the inner surface of the arm along the course of the axillary vessels. Minute petechial hæmorrhages were observed under the finger nails, but none could be detected under the toe nails. The patient's temperature was 102° F.; the pulse rate was 120 beats per minute; the systolic blood pressure was 140 and the diastolic pressure 90 millimetres of mercury.

Two days after the patient's admission to hospital her mother volunteered the information that the child had been attacked by a rat while asleep about two months previously, approximately a week before the onset of the pain and about a month before the sore throat and rash. The child had awakened to see the rat escape and had found that a

pimple on the left side of her face had been scratched. The blood from this scratch was washed away immediately and the wound caused had healed perfectly. No sign of it could be detected on her admission to hospital, and at the time the significance of this information was not realized.

The patient's general condition remained fairly good for five days; the pain and swelling in the arm disappeared after the administration of salicylates for two days after her admission to hospital, but a high temperature, swinging between 100° and 105° F., persisted. "M & B 693", in doses of two tablets every four hours, was given for forty-eight hours, but was discontinued owing to the patient's intolerance of the drug. Examination of the urine on September 5 revealed a very few red blood cells, a few hyaline and granular casts, and a few epithelial cells. A blood examination on September 7 showed that the red cells numbered 3,950,000 and the white cells 18,600 per cubic millimetre, and the haemoglobin value was 75%. A blood film revealed pronounced polymorphonuclear leucocytosis. Attempts at culture from the blood made on September 5 and 11 yielded no growth. On September 8 the patient's condition began to deteriorate rapidly; she became delirious, moist sounds appeared at the bases of both lungs, her systolic blood pressure dropped to 75 millimetres and triple rhythm appeared in the heart. On September 10 changes consistent with blockage of the arterial circulation were found in the foot and the lower half of the right leg. By September 12 the circulation in the leg commenced to reestablish itself, but the patient died later in the day. The temperature chart during the course of the illness is shown in Figure I.

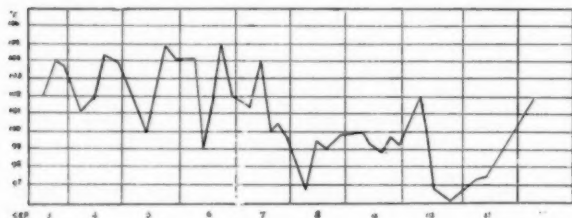


FIGURE I.
Temperature chart.

Post-Mortem Examination.

A post-mortem examination was made about twelve hours after death. The body was that of a well-developed, well-nourished young girl. The heart did not appear to be greatly enlarged in size; there was a slight amount of free fluid in the pericardium. On the mitral valve there was a large vegetation, three centimetres in diameter, the superficial half of which broke on being handled. This vegetation had ulcerated through the cusp onto the upper part of the ventricular wall (see Figure II). No other abnormality was



FIGURE II.
Photograph showing the vegetation on the mitral valve.

detected in the heart. The lungs were oedematous and collapsed, and numerous subpleural haemorrhages were noted. There was a considerable amount of fluid in the left pleural cavity and a moderate amount in the right pleural cavity. The spleen was greatly enlarged, with numerous infarcts,

which appeared to be breaking down. No abnormality was detected in the other organs. An attempt to find a clot in the anterior tibial artery was unsuccessful.

Bacteriological Findings.

Material was obtained from the vegetation on the mitral valve. Microscopic examination of smears from this material revealed masses of slender Gram-negative bacilli; these were highly pleomorphic in appearance, some organisms being filamentous, some curved, some with fusiform swellings, and others very small in size. Fibrinous material was present, but there was very little cellular reaction.

The appearance of the organisms suggested the possibility that they were either para-influenza bacilli or *Streptobacillus moniliformis*. Accordingly, inoculations were made onto sheep's blood agar, Fildes agar and ordinary agar and in 15% horse serum broth. Portion of the vegetation was also emulsified in broth and injected into the left hindfoot pads of three white mice. After three days' incubation no growth was present in the inoculated media; this pointed to the unlikelihood that the organism was a para-influenza bacillus. Five days later the inoculated feet of the mice were observed to be swollen and red. In a post-mortem examination of one of these mice pus cells and slender Gram-negative bacilli were seen in smears made from the pus from the affected ankle joint.

The remaining mice were given to Dr. Stephen Williams, of the Commonwealth Serum Laboratories, and to him we are indebted for the following report:

On the day the mice were received one mouse was killed and a small quantity of pus found in the ankle joint of the inoculated hind foot. Direct smears of this pus showed large numbers of slender Gram-negative bacilli, measuring approximately 3µ in length. Cultures were made from the pus onto ordinary agar, plain broth, and these media enriched with 30% normal horse serum. In 48 hours a good growth had occurred with the serum media while none appeared in the unenriched media. On serum agar the colonies were small (0.2-1 mm. in diameter), transparent and sticky. The broth cultures were typical of *Streptobacillus moniliformis*, showing what Topley and Watson (1936) describe as a fluffy, granular growth like bread crumbs, settling in the bottom of the tube. Stained films of the cultures showed filamentous masses fragmenting into bacillary forms and possessing the characteristic fusiform swellings. Further inoculations of white mice were made with pus and cultures, using the subcutaneous route in the foot pads. These mice all died within a fortnight of a generalized disease affecting several joints.

Unfortunately the strain was lost before further work could be carried out; but we believe that its identity with *Streptobacillus moniliformis* has been established. The reason for the non-isolation of the organism from attempts at culture from the blood made during life and from the attempts at culture made directly from the vegetation at the post-mortem examination may be found in the fact that the organism requires a high concentration of serum for its growth.

Discussion.

This appears to be the first recorded case in Australia of a human infection with *Streptobacillus moniliformis*, an organism which has been shown by Strangeways (1933) to be present in the naso-pharynx of a large proportion of normal rats. In America this organism is known as *Haverhillia multiformis*. Van Rooyen (1936) discusses the nomenclature in a recent paper. We have preferred the name *Streptobacillus moniliformis* as being more widely used in the English literature on the subject. The infection follows the bite of a rat, and a number of cases have been recorded in other parts of the world, particularly in America. From an epidemic disease in Massachusetts known as Haverhill fever, Parker and Hudson (1926) isolated the same organism, but were unable to implicate rats in the aetiology of the disease. For a recent review of the literature Farrell *et alii* (1939) should be consulted.

In the past, confusion over the aetiology of rat-bite fever has arisen owing to the implication of another organism, *Spirillum minus*, in such cases, particularly in Japan, where the disease is known as sodoku; but Allbritten *et alii* (1940) consider that the two diseases may be differentiated on clinical as well as on bacteriological grounds. These authors state that fevers due to *Streptobacillus moniliformis* are characterized by arthritis and a macular rash, that there may be no exacerbation at the site of the wound, that leucocytosis is common, and that the period of incubation is brief. It will be noted that the case here described presents all these features. In the sodoku type of fever the joints are rarely involved, a papular or large macular rash occurs, and exacerbation of the wound is almost invariable. The

mortality rate of the disease is usually given as about 10%. Blake (1916) reports a fatal case in a woman, aged sixty-seven years, and it is of interest to note that the clinical course of the disease closely resembled that in the case here described. The findings at post-mortem examination were practically identical, the main features in both cases being the endocarditis and the splenic infarcts.

The information concerning contact with the rat was offered voluntarily; but we have been unable to ascertain whether an actual bite occurred or merely a scratch. It seems certain, however, that the infection occurred by this route, as the first symptoms appeared within a week of the attack.

In view of the fact that diagnosis was established only post mortem, it seems likely that other undetected cases with recovery may have occurred in Australia.

Summary.

This paper records a fatal *Streptobacillus moniliformis* infection in a young girl following an attack by a rat.

Acknowledgements.

The authors are indebted to Dr. T. A. Heale for permission to publish the clinical history.

Bibliography.

- F. F. Allbritten, R. F. Sheely and W. A. Jeffers: "Haverhillia Multiformis Septicæmia: Its Etiologic and Clinical Relationship to Haverhill and Rat Bite Fevers", *The Journal of the American Medical Association*, Volume CXIV, 1940, page 2360.
 F. C. Blake: "The Etiology of Rat Bite Fever", *The Journal of Experimental Medicine*, Volume XXIII, 1916, page 39.
 E. Farrell, G. H. Lordi and J. Vogel: "Haverhill Fever: Report of a Case with Review of the Literature", *Archives of Internal Medicine*, Volume LXIV, 1939, page 1.
 F. Parker and N. P. Hudson: "The Etiology of Haverhill Fever (Erythema Arthriticum Epidemicum)", *The American Journal of Pathology*, Volume II, 1926, page 357.
 W. I. Strangways: "Rats as Carriers of *Streptobacillus Moniliformis*", *The Journal of Pathology and Bacteriology*, Volume XXXVII, 1933, page 45.
 W. W. C. Topley and G. S. Wilson: "Principles of Bacteriology and Immunity", 1936, page 274.
 C. E. Van Rooyen: "The Biology, Pathogenesis and Classification of *Streptobacillus Moniliformis*", *The Journal of Pathology and Bacteriology*, Volume XLIII, 1936, page 455.

Reviews.

LABORATORY METHODS USED IN NEW YORK.

In July, 1927, the methods in use in the Division of Laboratories and Research of the New York State Department of Health were collected and published in book form. A second edition of this book has recently appeared under a new title.¹ As the Director of the Division observes, there have been many changes in procedure during the past twelve years. Prior to their publication in 1927 these standard methods had been recorded in typewritten form for ten years, and had, of course, been subject to continual revision and improvement. The book is therefore an accumulation rather than a systematic text-book. In the introduction to the first edition it is pointed out that each series of methods is a unit in itself and does not necessarily conform to the others in arrangement or in the amount of detail it contains.

The instructions and directions for the media and glassware groups, for instance, are precise and somewhat elementary because the methods are intended for workers who, at first, as a rule are unfamiliar with laboratory regulations. The diagnostic methods are equally precise but they are focussed differently, being intended for workers with some experience in laboratory technique. The methods for the examination of water, sewage, ice and milk in the laboratories for sanitary and analytical chemistry are practically the same as those prepared by the American Public Health Association, and have merely been slightly modified to meet special conditions. The formulation of the methods used in the antitoxin, serum, and vaccine laboratories has presented a series of problems. The results of research . . . have necessitated repeated modifications.

The above quotation gives a fair idea of the scope of this book. The methods are described with great completeness and illustrated by photographs wherever possible. Chapters

¹ "Standard Methods of the Division of Laboratories and Research of the New York State Department of Health; Second Edition; 1940. London: Baillière, Tindall and Cox. Medium 8vo, pp. 681, with illustrations. Price: 41s. net.

describing the methods used in the administrative offices and in the research publications and library department are added. Appendices include the provisions of New York State laws and sanitary code relating to approved laboratories, to the handling of live pathogenic microorganisms or viruses, and to the collection of specimens for transmission to laboratories. Lists of references are appended to each chapter. The book is an official document rather than a text-book. On the whole, however, it is an efficient production, and should be of use to the directors of laboratories, in the training of technicians, the assembling of apparatus, and the general arrangements of a laboratory.

"PYE'S SURGICAL HANDICRAFT."

NEITHER the rumour of war nor war itself can stop the progress of "Pye's Surgical Handicraft". Adopting as its policy the supply in an accessible form of practical information required by the reader, the twelfth edition has appeared less than two years after its predecessor.¹

This book continues to fulfil admirably its subtitle as a "Manual of Surgical Manipulations, Minor Surgery, and other Matters Connected with the Work of House Surgeons and of Surgical Dressers".

We have found here clear descriptions of technical matters not otherwise available in a fairly extensive library. The use of lipiodol for seminal vesiculography and salpingography is one example, while the description of the use of the Muller-Abbott tube is very good indeed. Fractures are given the prominence they deserve in a work intended for house surgeons, and, as everywhere in this book, the methods advocated are sound and yet simple.

We were sorry to note the continued advocacy of prolonged pre-operative preparation of the skin. There is, we believe, much practical experience to reinforce the theoretical reasons why skin preparation must be limited to the period shortly preceding an operation, if maximum effect is to be attained.

The illustrations are profuse and excellent, and the general format of the book is all that can be desired. Fortunate indeed would be the visiting surgeon whose "resident" knew even half of what is contained in this treasury of knowledge.

BLOOD GROUPS AND BLOOD TRANSFUSION.

THE second edition of Wiener's book "Blood Groups and Blood Transfusion" is considerably larger than the first and maintains its excellent standard.² Dr. Wiener expounds the principle of blood groups, and supports them by facts and figures, and demonstrates them by detailed descriptions of technique, so that the book is of value to the clinician, statistician and experimental worker alike.

The chapters on the technique of the tests, the subgroups and the sources of error, are of particular value to the experienced worker who recognizes occasional anomalies in routine testing, as the text affords lucid explanations and is well illustrated by records from Dr. Wiener's wide experience.

The discussion on the indications for blood transfusion introduces some debatable points. The suggestion that a diastolic blood pressure of 40 millimetres of mercury or under is an immediate indication rather misses the point, as shock would have been manifest earlier and fluid therapy instituted. The doses of blood mentioned in treatment of diseases of the new-born are much smaller than those in use in Australia; and blood transfusion in the leuchæmias is mentioned only to be condemned.

The technique of blood transfusion is described in detail, and many mechanical ingenuities are illustrated; but the author wisely states that the simpler methods, calling for less manipulation, are attended by less risk. The principles of "drip" transfusion are discussed, also the difficulties of maintaining a "blood bank". The suggestion is made that 5-4% glucose should be added to citrate solutions used in the storage of blood (a recent article by Colonel Whitby *et alii* in *The Lancet* confirms this); but the author believes

¹ "Pye's Surgical Handicraft: A Manual of Surgical Manipulations, Minor Surgery and Other Matters Connected with the Work of House Surgeons and of Surgical Dressers", edited by H. Bailey, F.R.C.S.; Twelfth Edition, fully revised; 1940. Bristol: John Wright and Sons Limited. Demy 8vo, pp. 595, with illustrations. Price: 21s. net.

² "Blood Groups and Blood Transfusion", by A. S. Wiener, A.B., M.D.; Second Edition; 1940. London: Baillière, Tindall and Cox. Super royal 8vo, pp. 323, with 52 illustrations. Price: 27s. 6d. net.

that this solution should be replaced by Locke's fluid. In a series of 12,000 transfusions 13 deaths were due to wrong matching, and there were 0.08% of "unavoidable" deaths.

The reactions to and complications of blood transfusions are dealt with, and the point too little appreciated by the clinician is well taken, namely, that post-transfusion shock more frequently follows the use of the so-called "universal donor" than that of a donor of the same group as the patient. While minor reactions due to faulty preparation of apparatus, particularly rubber tubing, are described, no mention is made of the necessity for triple glass distilled water in the preparation of citrate solutions.

The chapters on genetics and biometrics are full and complete and lead to a description of the newer knowledge of the M and N factors of Landsteiner and Levine which is most illuminating. The possible fallacies in this work, calling as it does for animal antiserum and human red cells, are stressed as a warning to the inexperienced worker.

The search for association between blood groups and disease has not produced any positive evidence, and the writer spends little time on the subject, except to state that some surgeons believe that skin grafts from persons of the same group as the patient "take" better than those from another group.

The final chapters on the application of blood grouping and diagnosis of stains in legal work are most valuable. The laws which govern the possible group of an offspring, where the groups of the parents are known, make it possible to disprove paternity in 18% of cases, and if M and N factors are known, in 30% of cases.

In some few instances it is possible to offer positive proof of paternity, though by no means as often as it is sought. The author quotes the wording of the English law which empowers courts to seek such evidence as the tests may afford when necessary, together with statistics from American and European records.

The volume should be an admirable addition to the library of any laboratory, as well as to the bookshelf of the experimental worker.

VIRUS DISEASES OF MAN.

Virus diseases comprise only a relatively small proportion of the infections to which the human species is subject. Even so, it is an ambitious undertaking to attempt a compilation of all the relevant clinical and experimental data concerning them. In "Virus Diseases of Man" van Rooyen and Rhodes, of the University of Edinburgh, have carried out this task competently and successfully.¹

The introductory chapters provide a useful account of the various technical methods employed for the isolation and study of viruses. These are critically discussed and their limitations clearly stated. The bulk of the book is concerned with the details of published work on the human virus diseases. As the authors point out, the amount of space devoted to each disease is determined more by the volume of literature on the subject than the intrinsic importance of the disease. Vaccinia virus, which has always been a favourite object of study by virus workers, therefore receives more attention than is devoted to measles, mumps and chickenpox together. Rabies, which nowadays is only a matter of academic interest in Britain and Australia, is likewise treated at great length. However, it is probably correct to say that the whole body of virus research has grown up from the pioneer work of Jenner and Pasteur on these two viruses, and no one will grudge the space given to their discussion. Other major sections concern yellow fever, poliomyelitis and influenza. An interesting feature of the yellow fever section is a comprehensive account of the history of the disease. The less important virus diseases are all well discussed with extensive bibliographies. A careful reading of the chapters on subjects with which we are familiar convinces us that practically nothing of importance published up to 1939 has been overlooked. About 6,000 references are given, in itself an indication of the work involved. The only criticism we have to make is the failure here and there to indicate that certain of the claims of the transmission of some of the more obscure viruses to laboratory animals have never been confirmed. The authors, for instance, accept the claim by Japanese workers to have transmitted the virus of chickenpox to chick embryos and rabbits. Such inclusion of

¹ "Virus Diseases of Man", by C. E. van Rooyen, M.D., and A. J. Rhodes, M.B., Ch.B., M.R.C.P.E., with an introduction by T. J. Mackie, 1940. London: Humphrey Milford; Sydney and Melbourne: Cassell and Company. Medium 8vo, pp. 967, with illustrations.

questionable data is naturally inevitable in any comprehensive compilation, and to err in this direction is certainly preferable to the opposite fault of omitting important work which for the moment appears at variance with the authors' opinions.

A special word of praise is due to the care with which both contents and index have been arranged to make it particularly easy to find at once what is required. In all respects this is a first-class reference book.

THE STORY OF CHEMOTHERAPY FOR THE LAYMAN.

SINCE the discovery of the chemotherapeutic properties of para-amino benzene-sulphonamide in 1935, many short articles on chemotherapy in general have appeared in medical journals. In a small book called "The Conquest of Bacteria",¹ by F. Sherwood Taylor, the story of chemotherapy is told by a chemist in a form suitable for the lay reader. Commencing with an account of the germ theory of disease the author describes the body's defences and the use of inoculation, vaccination, antitoxin and therapeutic serum. He goes on to describe the earliest attempts to kill parasites within the body, and the history of chemotherapy from Ehrlich to Domagk and the great fine-chemical firms, or, as the subtitle of his book has it, "from 606 to 693". The book is readable and informative and should be much appreciated not only by the intelligent layman, but by the medical practitioner whose knowledge of the chemistry of therapeutics needs brushing up. It is, of course, a bare outline of the subject, and belongs to the realm of journalism rather than that of science. It is very good journalism, but it is in no sense a text-book; no references are given, and it possesses neither bibliography nor index. In his account of diseases in which chemotherapy is useful, the author's statements are often so superficial as to be inaccurate; but perhaps this is inevitable in a book of this kind. Simplicity and brevity are not always compatible with accuracy.

In the final chapter, entitled "The Need for Research", the author points out that hitherto research in chemotherapy has been left to the great fine-chemical firms. This raises difficult questions that have a place in a book such as the author has written. While the issues are far too involved for discussion in a short review, the author's ideas on this subject are stimulating; but they will probably have no great appeal to the average non-medical reader.

Notes on Books, Current Journals and New Appliances.

A BOOK ON DIAGNOSIS.

THE fifth of the "Practitioner Handbooks" entitled "Modern Diagnosis" has been published.² These handbooks have been published on behalf of *The Practitioner*, an English journal, well known to Australian doctors. They are edited by Sir Humphry Rolleston and Dr. Alan Moncrieff. Most of the chapters in the present volume have appeared as articles in *The Practitioner*, but the authors have revised the material and brought it up to date. In our opinion the most valuable part of this book is the first which deals with certain problems in clinical diagnosis, "a subject which is in danger of being neglected in face of the rising tide of scientific laboratory control". The following will have a special appeal to the general practitioner: "The Diagnostic Significance of the Knee Jerk", "Facial Diagnosis", "Diagnostic Importance of the Tongue", "Changes in the Nails as an Aid to Diagnosis", "Pains about the Head and Neck". This practical volume will surely have a large sale.

¹ "The Conquest of Bacteria. From 606 to 693", by F. S. Taylor, Ph.D., M.A., B.Sc.: 1940. London: Secker and Warburg; Australia: Angus and Robertson. Crown 8vo, pp. 144. Price: 10s. 6d. net.

² "Modern Diagnosis", edited by Sir Humphry Rolleston, Bt., G.C.V.O., K.C.B., M.D., F.R.C.P., and A. Moncrieff, M.D., F.R.C.P.: 1940. London: Eyre and Spottiswoode (Publishers) Limited. Demy 8vo, pp. 286. Price: 12s. 6d. net.

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All articles submitted for publication in this journal should be typed with double or treble spacing. Carbon copies should not be sent. Authors are requested to avoid the use of abbreviations and not to underline either words or phrases.

References to articles and books should be carefully checked. In a reference the following information should be given without abbreviation: Initials of author, surname of author, full title of article, name of journal, volume, full date (month, day and year), number of the first page of the article. If a reference is made to an abstract of a paper, the name of the original journal, together with that of the journal in which the abstract has appeared, should be given with full date in each instance.

Authors who are not accustomed to preparing drawings or photographic prints for reproduction are invited to seek the advice of the Editor.

VICTORIA AND THE AUSTRALIAN RED CROSS BLOOD TRANSFUSION SERVICES.

THE articles by Dr. Lucy Bryce and Dr. Rachel Jakobowicz recently published in this journal have directed the attention of medical practitioners once again to the valuable work on blood and blood transfusion that is being done in Victoria. The Australian Red Cross Society has been almost entirely responsible for the organization of effective blood transfusion services throughout the Commonwealth, and in this public service Victoria has taken the lead. The Victorian division of the Society in all its work on blood transfusion enjoys the cooperation of the Walter and Eliza Hall Institute of Research in Pathology and Medicine. This work, which is of the greatest value and importance to Australia, is unique because of the association of Red Cross organization with the necessary research at a well-equipped and active institute. The result of this happy association has been the creation of a unit fitted to meet the needs either of peace-time or of war. The unquestioned efficiency of such a unit may explain why it is sometimes taken for granted and not given the recognition that is its due. Since this journal must plead guilty of this very fault, we propose to review the activities of the Victorian Red Cross Blood Transfusion Service and of the services in the other States and to lay emphasis on the features that are making them so valuable at the present time.

The service was inaugurated in 1929 by the Victorian Division of the Australian Red Cross Society. The administrative work is carried out and the records are kept at Red Cross headquarters. There is a "call office" for donors at the inquiry office of the Royal Melbourne Hospital; this is a twenty-four hour service. The medical examination of donors and all laboratory tests are carried out at the Walter and Eliza Hall Institute. The history of the service has been one of steady growth since its inauguration. What may be regarded as the first stage was from 1929 to 1938, when donors were supplied without charge to all the public hospitals in Melbourne. In 1938 the service was expanded and donors agreed to give blood to private patients, and the patients were asked to make donations according to their means towards the main-

tenance expenses of the service. At the end of 1938 the donors tested since the inauguration of the service numbered about 800, and there were about 250 on the active list. In February, 1939, there were 444 available donors, and the average number of calls per month for the previous twelve months had been between 30 and 40. In May, 1939, what may be called the third stage in the development of the service was reached, for at this time a scheme was drawn up in anticipation of a war emergency, and the number of donors was considerably increased. At the end of September, 1940, the number of available donors was 2,815 and the average number of calls per month for the previous six months had been 200. For example, during the month of September, 1940, the number of calls was as follows: for individual transfusions at public hospitals, 38; for individual transfusions to private patients, 14; for the blood bank at the Royal Melbourne Hospital, 32; for serum to be stored at the Royal Melbourne Hospital, 19; for serum to be stored for army purposes, 88; for serum to be used for the purposes of blood testing, 6. Incidentally it may be mentioned that a blood bank was established at the Royal Melbourne Hospital in 1938. The cost of this bank was largely defrayed by the Red Cross Society; the experimental work on methods of blood preservation and so on was carried out at the Walter and Eliza Hall Institute; and blood was made available for use in urgent cases occurring in Melbourne or nearer country centres. Since the outbreak of war and the inception of the war emergency scheme the service has been divided into two parts. The first is a permanent service consisting of donors willing to give blood for any purpose, civilian or military. The second is an emergency service of donors who prefer that their blood shall be used for military purposes only—for example, the provision of serum to be stored or for blood group testing. The size of this organization, its administration, and the large number of available donors (believed to be second in size in any one city within the British Empire, the largest being in London) justify the statement already made that this service is suited to the needs of either peace-time or war. It is in point of fact already being used in both civil and military practice; members of the community are being supplied with blood when they need it, and serum is being stored for the whole of the Australian Imperial Force. Attention may also be drawn to the care exercised in the selection and testing of donors. The medical work has been done voluntarily, and chiefly by medical women at their own surgeries or at the Walter and Eliza Hall Institute; latterly it has been done at rooms in Collins Street provided by the Red Cross Society. Dr. Lucy Bryce is the Honorary Medical Officer in charge of the service. Each volunteer is subjected to a routine physical examination and his or her suitability to act as a donor is assessed. The blood group (or subgroup if necessary) is determined, the serum titre of iso-agglutinins and the haemoglobin are estimated, and the blood is subjected to the Wassermann test. No volunteer is accepted if the medical history or the routine examination reveals serious defects, if he or she is of unstable temperament and if his or her veins are unsuitable; the haemoglobin must not be less than 11.9 grammes per 100 cubic centimetres (85%). No donor is called upon to act more often than once in three months, and all donors are reexamined at

intervals if they have given blood on many occasions. It is gratifying to note that by far the greater part of the work has been done voluntarily—the donors have given their blood, the medical examiners have given their services, and even the junior laboratory assistants have done overtime work as a voluntary service. Among the salaried members of the staff of the Red Cross Society is one graduate who assists in the carrying out of blood tests; there are also two salaried officers on the clerical and administrative side.

The Blood Transfusion Service in Western Australia is really an offshoot of the Victorian service, and has made steady headway since the Red Cross Society in 1935 undertook to maintain a roster of donors that was already in existence at the Perth Hospital, and to keep a statistical record of transfusions. Up to 1939 approximately 1,000 transfusions had been given. It was then intended to enlarge the scope of the organization to provide donors for private patients in addition to those in public hospitals. However, when war was breaking a complete scheme for a permanent transfusion service was drawn up, and the Western Australian Division of the Red Cross at the request of the State Coordination Committee accepted the responsibility of implementing it. At Perth and at Northam 1,200 donors have been enrolled. Further, by collaboration between the Red Cross Society and the Perth Hospital, a blood bank has been established at the hospital. At the present time the needs of public hospital patients, private patients and patients in military hospitals are being met; but in the event of a national emergency the service would need to be expanded in all its aspects. It is perhaps most significant that those working hardest in the present service realize that Western Australia suffers from the lack of research institutions such as those found in other States. Until this gap can be filled progress will continue to depend on individual effort; but in spite of the gap Western Australia may be proud of what it has done.

At Adelaide the South Australian Division of the Red Cross Society has since the outbreak of war established an emergency blood transfusion service; it has been modelled largely on the Victorian service. So far 400 donors are on the list and an effort is being made to establish a blood bank at the Royal Adelaide Hospital. The military authorities have also asked the workers at the Institute of Medical and Veterinary Science to prepare dried serum for dispatch to the forces overseas. Here again we have the association of the Red Cross Society and a well-equipped and vital research institute, and progress will surely be made. In passing, it should be noted that heretofore excellent work has been done by the South Australian Blood Donors' Association. Since the foundation of the association in 1935 no less than 940 donors from this body have given blood. This work is generally recognized and will not be forgotten when it is coordinated with that of the Red Cross Society and when the whole organization is in the hands of the latter body as it probably will be.

In Queensland there is a small blood transfusion service and it is in the hands of the Queensland Division of the Red Cross Society. Progress has been slow and the service is being reorganized so that it may meet civil needs and be capable of immediate expansion as an emergency service. In Hobart there is a blood transfusion service that

has been organized by the Tasmanian Division of the Red Cross Society; 50 donors are available. The service which an influential committee in New South Wales has tried to launch is to follow the Victorian lead and be placed under the control of the Red Cross Society.

From the foregoing it is clear that the Victorian Red Cross Blood Transfusion Service is not only doing work of the greatest value to Australia, but has set up a model that has been copied by most of the other States. The most outstanding feature of the Victorian service is the enthusiasm of its workers, and herein lies the secret of its success. By placing its blood transfusion services, under the care and control of the Red Cross Society, Australia is doing what many other countries of the world have done. Even if some of the inhabitants of this globe are intent on slaughter, there are always some whose mission is the saving of life and who pursue this mission with courage and devotion.

Current Comment.

RESPIRATORY INFECTION AND ASTHMA IN CHILDREN.

THAT there exists an intimate relationship between juvenile asthma and infection of the upper or lower respiratory tract cannot be doubted. Of course there are many other aetiological factors of importance in this troublesome disease, and all too often several of them appear in the one child. Of outstanding significance among them is the hyperexcitable and overactive mind and body. In some children sensitivity to specific allergens dominates the picture. In others a chronic intestinal indigestion is most prominent. If, however, one has the opportunity to see many of these children, one does not need to be a very astute observer to realize how big a part respiratory tract infection plays: how often the asthmatic attack is preceded by an acute respiratory infection—a cold or an attack of acute bronchitis; how often the asthma has its onset after a severe chest infection, particularly whooping cough or measles with respiratory complications; and how often the child with asthma is found to have a chronic infected condition of the nasal sinuses or bronchial tree or both.

In 1939 Jean Crump¹ laid stress on this question of infection in juvenile asthma. She stated that "chronic bronchial infection plays an important role in nearly every case of asthma in which involvement is severe enough or has lasted long enough", a somewhat ambiguous statement. Be that as it may, the infection was there, and Crump resolved to treat it by means of autogenous vaccine. In a series of 112 cases bronchoscopy was carried out to confirm the condition of chronic tracheo-bronchitis and to obtain uncontaminated material for the preparation of a vaccine. The predominating organisms were various strains of non-haemolytic and haemolytic streptococci and staphylococci. Such a vaccine was given to the whole group. Each child was also submitted to oto-rhinological examination and extensively tested for sensitivity to the usual foods and inhalants. When these investigations revealed obvious disease or marked sensitivity, operation or desensitization respectively was used. The absence of a control group and the use of these accessory modes of treatment to some extent, but by no means entirely, destroy the scientific value of the survey. In many cases, it must be remembered, several factors contribute to the asthmatic attack, and it is unreasonable to expect treatment of one factor to effect a cure while the others remain active. Thus a number of children in the series whose condition had been little improved by desensitization to a specific allergen were greatly benefited by a further course of desensitization and in addition autogenous vaccine. In 27 patients

¹ American Journal of Diseases of Children, October, 1939.

there was no indication for any treatment except the vaccine. Of these 23 obtained complete relief, the condition of one was greatly improved and three were afforded doubtful benefit. On the whole Dr. Crump's results were very gratifying, and they bear out the truth of her original assumption that respiratory tract infection plays an important part in maintaining the asthma in the children. She does not advocate the routine use of bronchoscopy in asthma, but she does stress, and wisely, the need to treat its infective element.

A rather different approach has been made more recently by Lee Bivings,¹ who was impressed by the number of children in whom the symptom of wheezing accompanied respiratory tract infection. It is an unquestionable fact that acute bronchitis or tracheo-bronchitis in young children is often accompanied by expiratory wheeze and inspiratory recession of the soft parts of the chest, but it is not typical asthma. If the larynx too is involved the distress may closely resemble that seen in laryngeal diphtheria. (See the description of acute laryngo-tracheo-bronchitis given by Felix Arden in this journal of October 12, 1940.) The group of 225 children whom Bivings discusses were rather sufferers from chronic upper respiratory infection. It must be stressed that this is a common and important disease of childhood. There is a cough, often severe and even paroxysmal in character, occurring in the early morning and at night, and rarely during the day unless after severe exertion. The breath is offensive, the general health poor, and profuse night sweats, slight fever and abdominal pain are common. If the condition persists for long, chronic bronchitis is prone to follow. Examination reveals a congested nasal mucosa with a coating of muco-purulent secretion. The same secretion is seen behind the palate in the post-nasal space, or even dropping into the pharynx. The pharyngeal mucosa is reddened and islets of lymphoid tissue are prominent. Laboratory investigation reveals a secondary anaemia and a slight leucocytosis but no eosinophilia. The infecting organisms are most often streptococci or staphylococci. In 35% of these children attacks of wheezing occurred, but, insists Bivings, the condition is not asthma. The attacks differ from asthma in being continuous rather than paroxysmal, in the constant presence of local infection, in the absence of eosinophilia and evidence of specific sensitivity and in the failure to respond to adrenaline. The treatment recommended is a generous diet with iron and thiamine hydrochloride (vitamin B₁), nasal drainage by means of ephedrine tampons and the use of an autogenous or stock vaccine. Sulphanilamide was found to be of little use. Tonsillectomy too had little effect. We would suggest that antnal lavage, if indicated, is a valuable first step in nasal drainage. Bivings concludes that "the frequency of occurrence, the winter-time incidence, the presence of fever, the constant presence of infection, the absence of eosinophilia and the response to specific vaccine therapy would seem to entitle this clinical syndrome to a place of its own in paediatric practice, making it amenable to the care of any paediatrician and separating it from the field of allergy except when it occurs in the asthmatic in spite of the asthma and not because of the asthma". In emphasizing this clinical entity Bivings has done real service. It is interesting to speculate why only 35% of his patients had wheezing. Had they in fact become allergic to the products of their bacterial infection, and could their attack therefore be regarded as asthmatic? For the moment, however, that is not the point. What does matter is that chronic upper respiratory infection in children is a very common occurrence, and that "asthmatic bronchitis", as Bivings calls it, is primarily infective in origin, although there may be an allergic background which is a complicating or in some cases a predisposing factor. And as an infection it should be treated.

These two discussions leave little doubt of the importance of chronic respiratory infection in asthmatic or pseudo-asthmatic attacks in children.

OCULAR MANIFESTATIONS OF RIBOFLAVIN DEFICIENCY.

RIBOFLAVIN, lactoflavin or vitamin B₂, is an important part of the vitamin B complex. It is identical with the yellow pigment present in Warburg's enzyme and with certain yellow-green fluorescent pigments in living tissues, and is essential for all respiration.

V. P. Sydenstricker, W. H. Sebrell, H. M. Cleckley and and H. D. Kruse¹ describe the ocular manifestations of "ariboflavinosis". The patients studied fell into two main groups. In the first group were 29 persons under treatment for nutritional disease; the majority of these had had pellagra. The second group consisted of eighteen hospital employees (medical officers, nurses and technicians) who were apparently well nourished and provided with an apparently adequate diet; all but two of this group complained of cheilosis or of visual disturbances such as photophobia, dimness of vision or "eyestrain" not relieved by correction of refraction. These symptoms were displayed also by the patients in the first group and in these, in addition, there occurred extreme photophobia with blepharospasm, "roughness" of the eyelids and extreme visual fatigue. Superficial nebulae, seen grossly as slight "steaminess" of the cornea, were present in eighteen instances. Frank iritis occurred in four patients and mydriasis was also seen. The authors intend to make the incidence and behaviour of mydriasis and of disturbances of accommodation the subject of a separate report. Cataract was observed in six of the group, all elderly persons. The results of treatment with riboflavin were dramatic. The authors claim that every one of these forty-seven patients with ocular symptoms and signs was cured by the administration of riboflavin. The ocular symptoms were frequently those hitherto attributed to vague factors such as "toxic states", "focal infection" and "eyestrain". The dosage of riboflavin was from 5 to 15 milligrammes daily, administered in tablets or capsules containing one milligramme. Three patients were treated during certain periods with a solution of riboflavin in 65% propylene glycol injected intramuscularly. The doses mentioned are large; it has been calculated that the average daily requirement of riboflavin for adults is two to three milligrammes, the natural sources of this substance are yeast, certain vegetables, milk, liver and kidney. One kilogram of dried yeast contains only 20 milligrammes of lactoflavin; one kilogram of whey contains one milligramme. It would seem, therefore, to be difficult to administer large doses of riboflavin by dietary means. One interesting point is that riboflavin undergoes rapid changes when exposed to the light. The question arises whether this accounts for the prevalence of eye troubles in persons exposed to the glare of strong sunlight. The subject should be of special interest to Australians. The authors' observations were made in Georgia, one of the most southern of the United States, and they express the opinion that riboflavin deficiency is possibly the most prevalent apparently uncomplicated avitaminosis. Their paper is an excellent one; several case histories are given in detail and illustrated by photographs and diagrams. It is well worth a close study.

AN HONOUR FOR DR. JOHN ECCLES.

DR. JOHN ECCLES, Director of the Kanematsu Institute, Sydney Hospital, well known for his work on the central nervous and muscular systems, has been elected a Fellow of the Royal Society. The medical profession throughout Australia rejoices that another Australian graduate has been so honoured, and offers to Dr. Eccles its sincere congratulations.

¹ *The Journal of the American Medical Association*, October 26, 1940.

¹ *The Journal of the American Medical Association*, June 22, 1940.

Abstracts from Medical Literature.

GYNÆCOLOGY.

Retrodisplacement of the Uterus in Relation to Pregnancy.

A. H. ALDRIDGE, from the Women's Hospital, New York, discusses retrodisplacement of the uterus in relation to pregnancy (*American Journal of Obstetrics and Gynecology*, September, 1940). The author considers the technique and end results of the Bissell operation. In the Bissell operation the aim is to restore the round ligaments, the broad ligaments and utero-sacral ligaments to their normal functions. The author believes that owing to the altered blood supply and resulting congestion of the adnexa there is reduction in the total number of ova produced; if ova are produced, they are not perfect and lack qualities necessary for mature development; an abnormal endometrium unsuitable for nidation results. In the presence of uncomplicated chronic retroversion the lumina of the Fallopian tubes are often occluded or obstructed. In a small series 42% showed occlusion. For sterile women with retroversion who have disturbances of their menstrual cycle and evidence of tubal occlusion or obstruction, active treatment is indicated. In the author's opinion the use of the pessary should be limited to the prevention of chronic retroversion in post-abortional and post-partum conditions. The failure after operation would probably be less if conception did not occur for six months.

Dangers and Uses of Radium in the Treatment of Carcinoma of the Uterus.

MAURICE D. SACHS (*Western Journal of Surgery, Obstetrics and Gynecology*, October, 1940) remarks that most cancer institutions have replaced surgery by the combined use of radium and X-ray therapy, except possibly for a Stage I carcinoma of the cervix or malignant disease of the fundus. He stresses the importance of accurate application of the radium and emphasizes the dangers encountered. The London bomb type of applicators, with detachable handles, are favoured. On return to the ward the patient is placed in the semi-Trendelenburg position to remove the intestines from the source of irradiation. A retention catheter is used.

Adenosis of the Vagina and its Relation to Primary Adenocarcinoma of the Vagina.

THE history of adenosis of the vagina has been studied by A. Plant and M. L. Dreyfuss (*Surgery, Gynecology and Obstetrics*, December, 1940), who report three cases, stating that no other case has been reported in the American literature. They state that the abnormality is very rare. In all, some fourteen cases have been reported. Adenosis of the vagina results from differentiation of Müllerian vaginal cells. The glands resemble cervical glands. In the early phases the vaginal glands are completely covered by the normal squamous surface epithelium of the vagina, and there are no symptoms. When the surface is destroyed, discharge, contact bleeding and a feeling of heat in the vagina result. The condition is not found in children. The

authors state that primary adenocarcinoma of the vagina in most instances probably originates from adenosis.

Pregnandiol Excretion following Bilateral Oophorectomy in Early Pregnancy.

G. E. SEEGER AND E. DELFS (*The Journal of the American Medical Association*, October 12, 1940) report the results of a study of the pregnandiol excretion throughout pregnancy in a woman from whom all ovarian tissue had been removed on the sixty-third day of the gestation. There was no clinical abnormality during pregnancy or parturition. The pregnandiol excretion never rose above the level usually found during the first ninety days of pregnancy. The values were comparable with those found in the secretory phase of a normal menstrual cycle. In the authors' opinion the results of this investigation suggest that the corpus luteum hormone has an extraovarian source during the last two-thirds of gestation. The placenta is the most probable source. In the authors' case the placenta was of normal size and was producing normal amounts of chorionic gonadotropin.

OBSTETRICS.

Breech Delivery.

W. D. HAWKER AND S. D. SOULE (*Surgery, Gynecology and Obstetrics*, December, 1940) present the statistics of 291 breech deliveries from St. Louis City Hospital in a five-year period. Two-thirds of the mothers were multiparous. The fetal mortality in primiparous deliveries was 26.79%. In multiparous deliveries it was 28.85%. If prematurity (less than 2,500 grammes weight), maceration, stillbirths in which the fetal heart was not heard prior to labour, congenital anomalies, deaths after two weeks of life, and active syphilis are disregarded, the fetal mortality from breech delivery is reduced to 8.25% and 4.64% respectively. The maternal death rate was 0.34%. Lack of full dilatation of the cervix, lack of gentleness, and faulty judgement in method of delivery were responsible for fetal mortality.

Protein Diet in Pregnancy.

OLIN M. HOLMES (*Western Journal of Surgery, Obstetrics and Gynecology*, January, 1941) records the observations made on women and their infants when a diet rich in protein or comparatively poor in protein has been taken during pregnancy. A high protein diet is one containing 110 to 120 grammes of protein a day, and a low protein diet is one containing 60 to 70 grammes of protein a day. The number of women studied was 1,400, 700 being primiparae and 700 multiparae. All were given ample quantities of milk, green vegetables and fruit juices. Proteins were obtained mainly from meat, fish, eggs, milk and milk products. Where the low protein diet was given, the incidence of toxæmia among both primiparae and multiparae was higher than where the rich protein diet was given; but the incidence of prematurity in the group in which the low protein diet was given was only half that in the other group. Endeavours were made to limit the gain in weight (above the woman's ideal weight) to nine kilograms. This regulation of weight was

found easier when the diet was rich in protein. The women receiving a low protein diet tended to gain weight more rapidly. There was no appreciable difference in the average weight of infants, whatever the diet and whatever the mother's gain in weight. The author does not pretend to have made a scientific attempt to answer the question of what are the ideal protein requirements of the pregnant woman; he states that he has simply made a "tabulation of the clinical results found in a group of private patients with varying amounts of protein in their diets".

An Evaluation of the Effect of Antenatal Anti-Syphilitic Therapy on Fœtal Mortality and on Congenital Syphilis.

L. V. DILL, H. J. STANDER AND C. E. ISENHOUR (*American Journal of Obstetrics and Gynecology*, December, 1940), from the Cornell University Medical College and the New York Hospital, state that one of the greatest steps forward in the history of obstetrics was the advent of the treatment of syphilis in the pregnant woman. There is no room for doubt that adequate anti-syphilitic therapy instituted early in the course of pregnancy will greatly reduce the number of disastrous and infected products of conception. The only method the authors have considered as absolute in the diagnosis of syphilis in the fetus is a pediatric follow-up of six months or more. The X-ray findings in examination of the long bones, the placental histology, and the Wassermann test of the blood of the umbilical cord, are all used as a means of diagnosis; but none is specific. The Wassermann test seems only to be of value as an absolute diagnostic aid in congenital syphilis when the cord blood reacts and the maternal blood does not. It is recognized that a fetus whose cord blood does not react to the Wassermann test may develop syphilis. There may be no pathological changes of placenta or the long bones, and there may be no reaction to the Wassermann test, and yet the infant may be syphilitic. This series confirms the previous finding that a patient who receives more than four grammes of arsenic has less than a 5% chance of bearing a syphilitic child; but the administration of more than six grammes during the antenatal course does not absolutely insure that the fetus will be free of syphilis.

The Use of Solution of Extract of the Posterior Pituitary in Modern Obstetrics.

JOSEPH B. DE LEE, who writes in a symposium on the action of a solution of posterior pituitary extract (*The Journal of the American Medical Association*, October, 1940) wonders if the discovery of pituitrin has really been a blessing to medicine. Rupture of the uterus, laceration of the cervix and dead babies follow in the train of its use all too often; and this applies to many of the so-called combinations of this drug. There is an increasing demand among American women for "streamlined" labour, an unhealthy demand fostered by hysterical magazine and newspaper writers. Pituitary extract not only causes trouble from the intensity of contractions, but also in some patients produces a degree of shock. If, however, all the dangers are realized, De Lee believes that it is a blessing and has certain scientific

indications for its use. In septic abortion it is of value in aiding the expulsion of the uterine contents and in hardening the uterus during curettage. In labour the author commences with half a unit and then at the end of 20 minutes one unit is given; and then this dose is repeated every 20 or 30 minutes until some effect is seen. A total of 10 units is the maximum for one trial. In normal labour the author believes that it has no place. In atony, during the second stage, the author believes that an episiotomy and the application of forceps are safer for the mother and baby.

Veratrum Viride in the Treatment of Eclampsia.

R. D. BRYANT AND J. G. FLEMING (*The Journal of the American Medical Association*, October, 1940) report a series of 120 cases of eclampsia treated with *Veratrum viride*, with a mortality rate of 1.67%. In 1935 Bryant reported a series of cases, some of which are included in the present group. In the authors' opinion, as the result of the knowledge gained of the vasoconstriction of the entire arteriolar tree in toxæmia, the administration of *Veratrum viride* now has become a rational method of treatment. Their method was first to control the eclampsia, and when the toxæmia was under control, to induce labour. Ten minims of *Veratrum viride* were given immediately and repeated every ten to fifteen minutes until the pulse rate was below 60 per minute or the systolic blood pressure was below 120 millimetres of mercury. Thereafter, until the patient was conscious, doses of three to ten minims were repeated if the pulse rate rose to 80 per minute or the systolic blood pressure rose to 150 millimetres of mercury. When the patient had become conscious and cooperative, doses of three to ten minims were given if the patient had severe headache, pronounced visual disturbances or epigastric pain or convulsions. Intramuscular injections of magnesium sulphate were given, and 500 cubic centimetres of 20% dextrose solution were given intravenously every six to ten hours until consciousness occurred. The authors stress that the effect of a hypodermic injection of a therapeutic dose of *Veratrum viride* is startling and may cause undue alarm to those unused to it, and there is a well-marked individual susceptibility to the drug. Either morphine or atropine is an antidote; but neither was needed in this series.

The Recognition and Treatment of Foetal Heart Arrhythmias due to Anoxia.

C. J. LUND (*American Journal of Obstetrics and Gynecology*, December, 1940), working at the department of obstetrics and gynecology, University of Wisconsin, and the State of Wisconsin General Hospital, reports eight cases showing the results of the slowing of the foetal heart due to anoxia and the therapeutic response to specific oxygen therapy. One case was chosen to show the effect of nitrous oxide with too little oxygen. It was shown that the administration of a mixture of 70% of nitrous oxide and 30% of oxygen to the woman in labour had no effect on the foetal heart; but when the oxygen percentage was decreased to 15% it was noted that the foetal heart rate slowed to 90 beats per minute. When oxygen was given between contractions

the rate rose again to 135. If nitrous oxide and oxygen were given in concentrations of 90% and 10% respectively for longer than five minutes, foetal anoxia developed. The causes of anoxia come under two main headings: (i) failure of maternal supply, (ii) failure of the foetus to receive oxygen although the maternal blood stream is saturated with oxygen. Such factors might be due to disturbances of placental circulation or cord entanglement. However, in general, the response to oxygen therapy is rapid. The author concludes with the statement that early recognition of foetal anoxia and treatment by maternal oxygen therapy will prevent many cases of asphyxia neonatorum.

SURGERY.

Team Work.

IRVING WILLS AND ALBERT H. ELLIOT (*The Western Journal of Surgery, Obstetrics and Gynecology*, August, 1940) plead for closer cooperation between physician and surgeon in the care of patients. Rapid advances in medical knowledge have inevitably resulted in a greater division of labour. General nutrition, vitamin requirements, mineral storage and water balance are matters in which the physician may be of inestimable value to the surgeon in ensuring the least disturbance to the patient by operation and the smoothest possible convalescence. In intestinal obstruction, for instance, the question of acid-base balance, water balance and chloride loss are most important, and the physician can here be of great help. Patients suffering from metabolic disorders, such as *diabetes mellitus*, should obviously have the advantage of medical care in preparation for and following operations.

Carcinoma of the Breast.

A. ALDRIDGE MATTHEWS (*The Western Journal of Surgery, Obstetrics and Gynecology*, August, 1940) gives a review of aetiology and treatment of mammary cancer. He discusses the incidence in civilized and uncivilized races, white and black women, the parous and nulliparous, the breast which has given milk and that which has not. It is pointed out that cows never develop carcinoma of the udder. On the other hand, Bagg produced 78% of mammary carcinoma in mice by removing the young from the mother directly after birth; in a control group only 5% developed cancer. The author recommends that all mothers should be encouraged to breast feed their babies for six to seven months or till lactation ceases. Failing this, the breast pump should be used regularly till all the products of lactation have ceased to flow. It is also recommended that all women who are still menstruating when carcinoma develops should be subjected to artificial menopause and that no patient should become pregnant again after having had cancer of the breast. The treatment by surgery, radium and X rays and various combinations of these three is discussed. The author believes that a radical amputation should never be performed until confirmation by biopsy has been obtained. His own practice is to excise the suspected lesion with a large area of healthy gland and skin; a gross

examination is made in association with a pathologist and a frozen section of a suitable snipping made. Only then is the operative procedure decided on. The author describes Lee's method of X-ray treatment of the breast on two successive days, followed by radical operation in from two to four days' time. He does not use this method himself, but he does consider that X-ray treatment after operation may have value in certain cases of high malignancy, but should not be used as a routine measure. Radium combined with surgery has its place, as it may save life in certain cases in which invisible deposits might otherwise escape removal in the tissues just beyond the limits of surgical dissection. It is pointed out, however, that in no circumstances should the proposed use of irradiation lead to a less thorough operation than would otherwise be done.

Tetanus.

J. A. KIRTLLEY, JUNIOR (*The American Journal of Surgery*, September, 1940), reviews sixty cases of tetanus occurring during the last fourteen years in two American hospitals. They were classified arbitrarily into two groups, the early, in which the symptoms appeared within ten days of the injury, and the late, in which the incubation period exceeded ten days. These two groups were almost equal in number, and the mortality of the early group was 72% and of the late group 18%. The combined death rate was 47%. The commonest causes were punctured wounds from thorns, nails, splinters and rake prongs. Less commonly the original wound was lacerated or crushed. Three patients had received prophylactic injections of at least 1,500 units of antitoxin within twenty-four hours of the injury. Two of these patients died and one recovered. It is noted that all three patients had fractures, two being compound. The author quotes other figures to show that 5% to 10% of tetanus patients have had prophylactic antitoxin. While comparable figures in civil life are not available, the author recalls that in the Great War the incidence of tetanus was only 0.117%. He considers this to be a strong argument in support of prophylaxis. However, as tetanus patients who have had a prophylactic injection do not show a lowered mortality (in another series four out of five died) the author thinks that a critical study of the value of antitoxin is indicated. He suggests that tetanus toxoid, while not of service in the treatment of acute tetanus, may be adapted as a prophylactic agent, given either alone or with antitoxin. The author discusses at some length the treatment in tetanus of the local wound (if recognized and accessible) and quotes other writers to show that the mortality is less when the wound is incised and all foreign material is removed. In his own series the mortality in those patients treated by incision and cleansing of the wound was less than a third as high as in the remainder of the cases. He prefers the intravenous and intramuscular routes for the administration of antitoxin, and considers "Avertin" to be probably the best basal anaesthetic at present available. Phenol was given intravenously to seven patients, but the results were inconclusive. Signs and factors found to indicate a grave prognosis were an incubation period under one week, wounds on the face, trunk and upper extremities, high fever and tachycardia and convulsions.

British Medical Association News.

SCIENTIFIC.

A MEETING of the New South Wales Branch of the British Medical Association was held on October 24, 1940, at Saint Vincent's Hospital, Sydney. The meeting took the form of a number of clinical demonstrations by members of the honorary staff of the hospital. Part of this report appeared in the issue of March 15, 1941.

Surgical Treatment of Essential Hypertension.

DR. DOUGLAS MILLER discussed the records of a patient suffering from essential hypertension. The patient, a woman, aged thirty-six years, had been referred to the hospital by Dr. Bruce Hall. For four years she had suffered from severe headaches. During the past six months she had been dizzy and unable to do her ordinary work. The systolic blood pressure was 290 and the diastolic 150 millimetres of mercury. Investigation revealed that she had sustained no renal damage.

A two-stage bilateral intrathoracic resection of the splanchnic nerves and lower sympathetic trunk had been performed. The immediate post-operative fall of blood pressure had been to 120 millimetres of mercury systolic and to 80 millimetres diastolic; but during succeeding weeks the pressure had gradually climbed, and two months later it was 220 millimetres of mercury systolic and 120 diastolic. The patient was, however, completely relieved of her symptoms and was able to lead a normal life. Dr. Miller pointed out that this was a typical result, in that though objective improvement might not be very striking, properly selected patients nearly always experienced great subjective relief.

Lipoma.

Dr. Miller then showed a huge lipoma weighing nine pounds. This had been removed from the intermuscular region of the lower limb extending from the ischial tuberosity to below the calf. It had the sciatic nerve tightly stretched over it posteriorly, and rested on the *adductor magnus* and popliteal vessels anteriorly. The patient had experienced a slow increase in the size of his left leg for many years, until eventually his trouser leg could not be pulled on at all.

Vulvectomy.

DR. M. BRITNELL FRASER showed two patients on whom vulvectomy had been performed. The first had had simple vulvectomy for long-standing *leucoplakia vulvae*. Dr. Fraser showed that there was no disability after the operation and that the condition was completely cured.

For comparison, Dr. Fraser showed a second patient, aged fifty-six years, on whom he had performed radical vulvectomy with bilateral excision of the groups of inguinal glands for a proved carcinoma of the *labium majus*, which had supervened in spite of deep X-ray therapy for leucoplakia. Examination of microscopic sections revealed a squamous-celled carcinoma.

Dr. Fraser described his technique of operation. He said that he tied the internal pudendal artery at an early stage in the operation; this procedure made the subsequent dissection practically bloodless. He stressed the importance of an indwelling catheter for ten days after operation and of confinement of the bowels for at least five days. By these measures the edges of the wounds were kept dry and healing by first intention could be expected.

Carcinoma of the Cervix.

Dr. Fraser then showed a specimen of early carcinoma of the cervix, which had been removed by Wertheim's method of panhysterectomy. Dr. Fraser said that he favoured this method without pre-operative radium treatment only in very early cases.

Tubal Mole.

Dr. Fraser finally showed a specimen of a tubal mole with decidual reaction in the endometrium, the *corpus luteum* having a hemorrhagic centre. The ovary on the other side contained a benign papillary cyst adenoma.

Subdural Haematoma Surgically Treated.

DR. V. J. KINSELLA showed a female patient, aged sixty-six years, to illustrate the successful outcome of surgical treatment in a case of subdural haematoma. This was looked upon as being most important. Dr. Kinsella said that the condition was apt to pass unrecognized, for it was described either inadequately or not at all in surgical text-books.

Dr. Kinsella gave the clinical history of the patient shown. He said that she had begun to suffer from headache and later became unconscious thirteen days after a fall from which she had apparently completely recovered. The latent interval was important; with such a history a patient should be looked upon as suffering from a haematoma until it was proved otherwise. Albuminuria and glycosuria occurred in some of the more acute cases and should not distract from the diagnosis. In the case of the patient shown, tachycardia with a gross irregularity developed before operation and disappeared after operation. Dr. Kinsella stressed the following diagnostic points with regard to subdural haematoma: (i) A low pressure bleeding from cerebral veins might be present. (ii) Symptoms might be late in onset, perhaps weeks or months after the injury. (iii) Symptoms were often vague and unaccompanied by localizing signs, such as headache, convulsions, psychic changes, coma. (iv) Localizing signs might be absent. The commonest were those of involvement of the upper motor neurone. (v) The cerebro-spinal fluid might be stained with altered blood and the pressure might be raised, normal or low. (vi) An encephalogram or ventriculogram revealed signs of a space-occupying lesion. (vii) It was often necessary to make a small trephine opening, sometimes bilaterally, under local anaesthesia, to determine the diagnosis.

Hydatid Cyst of the Liver.

DR. R. J. TAYLOR showed a female patient, aged thirty-five years, who had suffered from pain in the right hypochondrium for five weeks and from tenderness in the right side of the back for the same period. The pain, which was sharp in character, appeared at any time and was not related to meals, exertion or breathing. It was present for anything from a few hours to a few days. The patient had suffered from measles in 1920 and had undergone appendicectomy and removal of an ovarian cyst in 1939. Her mother had died at the age of fifty-six years from "a ruptured artery in the throat"; her father had died at the age of seventy-four years from heart failure. The patient had lived at Gundagai all her life.

On examination of the patient fullness was noted in the right hypochondrium, the chest moved evenly on respiration and the border of liver dullness was raised. No abnormality was detected in the abdomen.

On October 2, 1940, an X-ray examination of the chest was made and the radiologist reported that there was no evidence of tuberculosis; the right dome of the diaphragm was elevated, and a cervical rib was present on the right side. On October 3 a blood count gave the following information: the erythrocytes numbered 3,600,000 and the leucocytes 5,000 per cubic millimetre; the haemoglobin value was 55% and the colour index 0.76; 5% of the leucocytes were eosinophilic cells. Microcytic hypochromic anaemia was present. On October 8 the Casoni test produced no reaction. On October 11 the precipitin test for hydatid gave negative results. On October 18 an X-ray examination of the chest revealed pronounced enlargement of the liver, with elevation of the dome of the diaphragm on the right side. There was no evidence of calcification in the liver; the spleen appeared to be a little enlarged.

A Case for Diagnosis.

Dr. Taylor then showed a male patient, aged seventy-four years, who had suffered from hoarseness for two months, from precordial and epigastric pain for seven weeks, from a feeling of "tightness" in the chest for seven weeks, from slight pain in the throat for two months and from dyspnoea when walking along level ground for two months. It was considered that the patient was probably suffering from either an aortic aneurysm or a mediastinal tumour. He had been well until two months earlier, when he suddenly lost his voice and became breathless on exertion, even when walking on level ground; seven weeks prior to the meeting he began to experience a dull pain over his chest and epigastrium, which was continuous and had become a little worse. The pain was aggravated by his lying on his back, but was unaffected by the taking of food or by exertion. His mother had died at the age of fifty-six years from a "tumour", and his father at the age of sixty-one years was accidentally killed.

When the patient was examined his pulse rate was found to be 88 per minute; the radial artery was tortuous. There was a harsh systolic murmur at the aortic area conducted to the neck and axilla. The blood pressure on both sides was 150 millimetres of mercury systolic and 100 diastolic. No tracheal tugging or displacement was present. Movement was diminished on the left side of the chest. Vocal fremitus was diminished on the left side below the clavicle, and there was an area of dullness to percussion below the left clavicle. The breath sounds in the left lung anteriorly were vesicular in type; there was a patch of bronchial breathing

below the clavicle. Posteriorly no abnormality was detected. The patient's blood serum failed to react to the Wassermann test. An X-ray examination revealed an aneurysmal dilatation of the aortic arch; the cardiac shadow was not enlarged. Fluoroscopic examination revealed slight pulsation and slight deviation of the oesophagus. The opinion of the radiologists was that the lesion was unquestionably an aneurysm.

Disseminated Sclerosis.

Dr. Taylor's third patient was a male, aged forty-seven years. Four years earlier he had begun to grow irritable and to go to bed tired and wake up tired. He then noticed that his legs were becoming weak and he began to stagger as he walked, drifting to the left. The ataxia was increased by his looking sideways or upwards. In 1938 he experienced difficulty in articulating words. In 1939 he began to suffer from frequency and precipitancy of micturition, passing urine ten times during the day and three times during the night; he also had periodic enuresis. In 1937 he began to suffer from nightmares, calling out in his sleep and falling out of bed; he had also become very "nervy" and emotionally labile. His headache was frontal in type and almost always occurred in the day-time. He had suffered from dyspnoea on exertion for three years and from occasional precordial pain on exertion. No abnormality of note was detected in the respiratory and alimentary systems. Examination of the central nervous system disclosed weakness in the legs and ataxia; dysarthria was also noted. The patient had undergone appendicectomy in 1937 and an operation for haemorrhoids in 1938. His father and mother had died of pneumonia, and he had two brothers and four sisters alive and well. There was no family history of tuberculosis, cancer or insanity. The patient was a furnaceman; he did not smoke or take alcohol, and denied that he had ever had venereal disease.

When the patient was examined, right-sided facial weakness was noted and the tongue deviated to the left; the other nerves were intact. Motor power in the upper limbs was intact; that in the right leg was good, but weakness was apparent in the left leg. Babinski's sign was not elicited. The finger-nose test revealed an intention tremor on both sides, with gross incoordination; the heel-knee test revealed pronounced incoordination and an intention tremor on the left side; the test was fairly well performed on the right side. Dysdiadochokinesis was present and Romberg's sign was elicited. The superficial reflexes were all present and exaggerated. Sensation to touch with a pin-point and cotton wool was good. The finger writing test was well performed, and the sense of passive movements and position was good. There was no loss of discrimination between heat and cold, and stereognosis was good.

On October 15, 1940, hearing was slightly diminished in both ears. The drums were normal. Dr. Ramsay Beavis examined the patient's larynx and reported that movement of the right vocal cord appeared to be somewhat impaired. The optic fundi were normal. A blood count revealed no abnormality. The Wassermann test failed to produce a reaction. Dr. D. G. Maitland carried out a stereoscopic X-ray examination of the skull and reported that he had detected no definite abnormality.

Medical Societies.

MELBOURNE PÆDIATRIC SOCIETY.

A MEETING of the Melbourne Pædiatric Society was held on November 20, 1940, at the Children's Hospital, Carlton. Dr. H. DOUGLAS STEPHENS, the President, in the chair.

Atypical Scleroderma.

Dr. J. W. GRIEVE showed a boy, aged four years and three months, who for at least five months had had a scar on the left upper portion of the abdominal wall, which was becoming progressively larger. In other respects the boy was well. The scar was not due to injury or operation, and no facts had been elicited in the family history which threw any light on the matter. At the time of examination, on October 21, 1940, there was a localized area of atrophy of subcutaneous tissues, about the size of the palm of the hand, in the area of distribution of the eleventh dorsal segment, which extended from the middle line to several inches in front of the mid-axillary line. An area of wasting of subcutaneous tissues was also observed on the medial aspect of the left thigh, and wasting was present in the

region of the arch of the foot and to a less degree on the medial aspect of the leg. Muscular power and deep and superficial reflexes were not affected by the lesions. The left lower limb was found to be half an inch shorter than the right one; the shortening was confirmed radiographically.

Dr. Grieve said that the outstanding feature was the localized wasting of subcutaneous tissues. He thought that the case would interest the members as an example of lipodystrophy, atypical scleroderma or possibly a trophoneurosis. He had not encountered anything exactly like it before.

Dr. H. J. SINN said that the condition must be an unusual one if Dr. Grieve had not seen it before. It had reminded Dr. Sinn of the group of patients suffering from scleroderma who had been shown by Dr. Price at a meeting of the society about two years earlier (*THE MEDICAL JOURNAL OF AUSTRALIA*, Volume I, 1939, page 317). Scleroderma was rather an elastic term which apparently could include sclerosis of underlying subcutaneous fat, muscle or even bone. The aetiology was as obscure as the indications for treatment. A diversity of methods of treatment had been advocated; thyroid gland extracts and other hormones and even vaccines had been tried; and most of the *armamentarium* of the dermatologists had failed. The condition was likely to be slowly progressive and could lead to deformities.

Dr. Grieve, in reply, said that multiple localized scleroderma seemed to be the nearest diagnosis in the present case. Other subjects of scleroderma that had come under his notice had had more thickening of the skin and less striking loss of subcutaneous tissue. He said that he proposed to keep the boy under observation and report progress at a later date.

Bilateral Congenital Dislocation of the Hip.

Dr. W. KENT HUGHES demonstrated from skiagrams the late results of treatment of bilateral congenital dislocation of the hip. In one of the skiagrams he pointed out the features of dislocation of the hip at birth as a contrast to those of the congenital condition. From a series of films taken twenty-two years after operation, which was performed when the subject was aged eighteen months, he showed the evidence of the extraordinary damage to the epiphyses which had resulted from the use of force in reduction. The patient had presented himself to Dr. Kent Hughes that week, suffering from considerable pain. He could not flex the thigh on the abdomen beyond a right angle on the right side, and flexion of the left thigh was not much better; adduction also was limited. Dr. Kent Hughes commented that under general anaesthesia there had been no feeling of roughness or grating and the patient's range of movement was increased after manipulation; but he was going to try to improve matters by diathermy without performing any open operation.

Dr. Kent Hughes went on to say that ever since 1916 he had given up using force for reduction prior to the application of a plaster cast. If he could not reduce the dislocation readily, he put on the plaster cast in the best position he could obtain without much traction on the muscles, and after a while he did the same a second time and then a third time. By that method he had reduced one dislocation successfully when the patient was aged fifteen years, as long ago as 1920. The patient had continued to report to him for two years, and the result was satisfactory.

Dr. W. R. FORSTER said that he understood that Dr. Kent Hughes was advocating progressive reduction of the dislocation by repeated applications of plaster casts. Dr. Forster had almost abandoned that method if he failed to reduce the dislocation; it was surprising how quickly decalcification occurred in a plaster cast, and this led to fracture of the bone at subsequent manipulation. If the shaft was fractured the difficulties were increased.

Dr. J. G. WHITAKER said that he had had the opportunity with Dr. J. B. Colquhoun to examine the Children's Hospital records and to review the methods and the results obtained in congenital dislocation of the hip. He had gained the impression that the radiographic evidence was not a good indication of functional result; the head of the bone was usually "mushroomed", but in spite of that the function might be good. If the first attempt at reduction failed, it was rare to succeed subsequently. Dr. Whitaker did not object to dividing the adductor tendons in order to have the thighs flat on the table. The problem of anteversion of the neck was an awkward one. Subtrochanteric osteotomy was a useful procedure before reduction was attempted a second time. Dr. Whitaker was inclined to support Dr. Kent Hughes against Dr. Forster in the matter of securing the best position by means of plaster casts from time to time.

DR. H. DOUGLAS STEPHENS said that the risk of fracture could be avoided if the subsequent attempt was made about ten days or a fortnight after the previous one, instead of the interval's being prolonged to a month or six weeks. Anteversion of the neck was serious, and if it was pronounced the surgeon was foredoomed to failure; it was the exception to achieve good results on both sides in bilateral dislocations.

Dr. Kent Hughes, in reply, said that he was glad to have the support of Dr. Stephens and Dr. Whitaker. In his experience the adductor tendons were not so resistant as the hamstrings, but the hamstrings could not be cut without serious disability; the adductor tendons stretched readily enough, however. Dr. Kent Hughes commented on the degree of deformity of the head which could be associated with a good functional result. He referred briefly to the case of a girl who had so much mushrooming of the head that the leg was half an inch short; she could play tennis vigorously and had no apparent disability.

Ruptured Pulmonary Hydatid Cyst.

DR. J. G. WHITAKER presented a progress report on the case of a boy, aged nine years, with a single hydatid cyst in the right lung, who had been shown for Dr. W. W. McLaren at the previous meeting of the society by Dr. R. A. J. Stanton. A few days after that meeting the boy had become pale, had suffered from shock and had brought up blood-stained mucus; he had not, however, coughed up any material clinically recognizable as of hydatid origin. To judge by the skiagrams, the cyst had shrunk considerably in size, though a little diminished translucency was present laterally. Dr. Whitaker commented that in thousands of instances spontaneous cure must occur. Professor H. R. Dew, in his book on hydatid disease, with reference to deeply placed parabronchial cysts, had stated that cure would occur naturally in 80% to 90% of cases. In the present case it had been impossible to demonstrate communication with the bronchus even in skiagrams taken after the instillation of iodized oil. There were still some adventitious signs at the base of the right lung, but they were not regarded as of any great importance.

DR. W. R. FORSTER asked for information about the presence or absence of daughter cysts in hydatid disease of the lung.

DR. H. BOYD GRAHAM said that it was rare for cysts not to be sterile in childhood. He had had many interesting discussions on the subject with Professor Dew. The reasons advanced for the relative infrequency of daughter cysts in childhood were that the cysts were young and that unless they were in an exposed position the normal evolution of the parasite could proceed without interference. Professor Dew's interesting views on the development of daughter cysts, brood capsules and scolices were probably well known to the members of the society.

DR. ROBERT SOUTHEY recalled an instance in which a patient in the care of the late Dr. Hamilton Russell had had a long-standing cyst containing daughter cysts.

DR. H. DOUGLAS STEPHENS said that in such a case as the one under discussion an interesting problem was when should the surgeon decide to operate. Dr. Stephens had formed the opinion that rupture of a cyst could be precipitated by too much handling; he had seen examination of a patient by a series of students precede rupture, and he thought it probable that the presentation of the patient and the consequent handling at the last meeting of the society had had something to do with the rupture and discharge of portion of the cyst through the bronchial passages.

Atypical Sprain of the Ankle.

DR. J. D. BEGG showed a boy, aged eleven years, who had sustained an unusual injury in the region of the ankle joint. The child had not had any definite trauma; but after he had taken part in a "broad jump" at the school sports, a bony swelling was discovered which appeared to be exuberant callus from the posterior border of the tibia. It was difficult to elicit any tenderness even on firm pressure, and there was no swelling of the soft tissues. Dr. Beggs showed the skiagrams and asked for expressions of opinion concerning the origin of the abnormal structure and the treatment that should be undertaken.

DR. J. G. WHITAKER said that he thought a piece of the tibia had been torn off and had fused with the talus. He asked, however, to hear the opinion of Dr. Keith Hallam on the radiographic evidence.

DR. KEITH HALLAM said that the matter required much thought if an attempt was to be made to analyse origins. The films had been prepared seven to ten days after the alleged accident in jumping; Dr. Hallam did not think the bone arose either from the tibia or from the talus. The

origin was possibly from an *os trigonum*; but when the *os trigonum* was present it could usually be seen bilaterally, and in the skiagrams that had been shown it was difficult to be certain of the presence of an *os trigonum* on the unaffected side. It was necessary also to think of chondromatosis beneath the capsule and an aggregation of extra-articular bony masses. Dr. Hallam thought that the effort of jumping had drawn attention to a preexisting condition.

Dr. Whitaker postulated an analogy with a fragment from the elbow drawn by ligamentous attachments which became fixed in the new position and gave rise to grave disability.

Dr. Stephens thought a piece of the medial malleolus had been pulled off by the deltoid ligament, but he did not think the condition was chondromatous because of the amount of calcification that had occurred in so short a time.

Dr. Beggs, in reply, said that he had had under consideration a lesion of the *os trigonum*, and thought that, though not much ossification had yet occurred, he could discern an *os trigonum* on the opposite side. He was in agreement with Dr. Hallam's view that the jumping had only drawn attention to an abnormality that existed before. The later skiagrams had been prepared expressly to decide whether a fracture of the talus had occurred, and Dr. Hallam thought that the appearances were sufficiently clear to exclude that possibility. The boy had gone on with the jumping to the end. He used to ride a scooter, and had formed the habit of kicking back with the ankle, with resultant barking of the skin; he might in that way have produced a hematoma which was not noticed at the time, but which had calcified since and caused the lesion under discussion.

Vaccine Treatment of Chronic Respiratory Infections.

DR. W. McL. SMITHERS read a paper on the relationship of upper respiratory infection to chronic chest conditions and its bearing on vaccine treatment, and he showed three patients. He said that in childhood conditions such as asthma and recurrent bronchitis were usually secondary to the common cold, and chronic bronchitis and bronchiectasis were made worse by colds. Consequently he had attempted to see whether the incidence of colds in those pathological states could be reduced by vaccine treatment. He had used a mixed coryza vaccine by injection and found that a reduction in the incidence of colds had been obtained for at least a season and frequently for a year. He had also obtained good results with some oral vaccines, but the immunity was transitory and ceased as a rule as soon as the vaccine treatment was discontinued.

With reference to a group of patients with chronic or recurrent bronchitis, Dr. Smithers said that he had found the results very satisfactory, provided that a relationship could be established between the cold and the bronchitis. Failure was common in the children in whom malnutrition and poor hygiene were evident, and he made the suggestion that they had not the intrinsic vitality to produce antibody even under the stimulus of vaccine. Failure of vaccine treatment had also been established if the children had suppurative sinusitis; vaccines containing suppurative organisms had not yet been tried by him for the group.

Dr. Smithers showed a boy, aged seven years, who had suffered from frequent colds and bronchitis for four years and who had not had a cold or any chest trouble since he was given a course of vaccine treatment towards the end of 1939.

Dr. Smithers said that in children suffering from bronchiectasis the problem was one of avoiding reinfection, and the results had been very satisfactory. He showed a boy, aged eleven years, who had had an organic stricture of the left lower bronchus and who was known to have had bronchiectasis for five years; cough with sputum had been continuous and aggravated by frequent colds. In May, 1940, he had had a course of vaccine treatment, and since then, even throughout the winter, he had not had a cold, the cough and sputum had disappeared and there were no adventitious physical signs in the chest.

Dr. Smithers went on to say that children suffering from asthma were more difficult to treat and the results were less dramatic. It was necessary to select for vaccine treatment children whose asthma was secondary to upper respiratory infection, but to exclude those in that group who had attacks of asthma as the result of contact with kapok or from mechanical irritation. Even then, a proportion perhaps as high as 90% of children with asthma remained available for vaccine treatment, and in the treated group the frequency and severity of the attacks had been greatly reduced. Dr. Smithers showed a boy, aged eleven years, who had been subject to attacks of asthma approximately every six weeks; he had had no

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attacks since treatment with an oral vaccine had been commenced in February, 1940.

DR. MONA BLANCH said that she had concentrated her attention for a number of years on the investigation of the cause and treatment of asthma, but had found it very depressing work. The patients were prone to improve, only to relapse later. She had had some good results with vaccine, but not with catarrhal vaccine in asthma or bronchiectasis. She had a very limited experience of the results of oral vaccine and had probably not used the one that Dr. Smithers seemed to find satisfactory.

DR. ROBERT SOUTHEY said that he wished to refer to two points of importance. The first one was the association of sinus infections with chronic chest conditions and the recognition of the presence of upper respiratory infection; it was essential to success in treatment to have the suppurative sinusitis cleared up. The other matter was the question of dietary. There was no doubt that many children who suffered from chronic respiratory infection were receiving a deficient dietary with an over-abundance of carbohydrates. Dr. Southey went on to say that he wished to draw attention to the inference from Dr. Smithers's remarks, that a very low percentage of asthma was due to allergy. He reminded members of the way in which Dr. Mostyn Powell had shown how many allergic factors could be traced by careful detective methods after close history-taking; Dr. Powell's remarks had been published in THE MEDICAL JOURNAL OF AUSTRALIA, Volume II, October 17, 1936, at page 547. Dr. Southey said that he could recall four instances in the past twelve months in his own experience in which he had satisfied himself as to the cause; kapok, orange juice, a feather pillow and a cat had acted as allergens.

DR. H. J. SINN congratulated Dr. Smithers particularly on the way in which he had summarized the facts, and on his patent honesty in the matter. Dr. Smithers had made no sweeping claims, but had thrown out a few suggestions which should serve to revive vaccine treatment as an addition to other forms of therapy with the object of improving the results. Such treatment was based on secure theoretical grounds, even though admittedly it was difficult to assess the results. Dr. Sinn hoped that they would have a further report from Dr. Smithers and that he would continue the work at the hospital; the cost of the vaccines was justifiable if the expenditure brought about improvement in the treatment of such vexatious conditions as chronic respiratory infections.

Dr. Smithers, in reply, said that he was gratified by the kindly reception of his views. He was grateful to Dr. Southey for directing attention to the legitimate inference which could be drawn from his remarks; he had purposely avoided detailed reference to the allergic side of asthma, and he was only too pleased to concede the point that he had overstated the incidence of infection as a factor in the production of asthma. If asthma occurred in infancy, it was likely to have a specific cause; but the later the onset, the less probable it was that the specific factor would be the only and the important one. Dr. Smithers had been working with Dr. Powell for over two years and could say in his absence that Dr. Powell was swinging over to the view that, in a vast majority of cases, asthma was due to infective rather than to allergic factors. In conclusion, Dr. Smithers emphasized the importance of eliciting the fact that the attacks of asthma were usually preceded by a cold, and of using that time relationship as an indication for vaccine treatment.

Post-Graduate Work.

A COURSE IN UROLOGY AT SYDNEY.

THE New South Wales Post-Graduate Committee in Medicine will hold a course of instruction in urology at the Prince Henry Hospital, Little Bay, from May 5 to May 16, 1941. The programme is as follows:

Monday, May 5.

- 2 p.m.—"Urogenital Infections, Pyogenic and Specific": Dr. R. J. Silvertown.
3 p.m.—Operations: Dr. R. J. Silvertown.

Wednesday, May 7.

- 4.15 p.m.—"Obstructive Lesions of the Urinary Tract": Dr. R. G. Harris.

Friday, May 9.

- 9 a.m.—"History Taking and General Diagnosis": Dr. R. J. Silvertown.
10 a.m.—Ward rounds: Dr. R. J. Silvertown.

Monday, May 12.

- 2 p.m.—"Urinary Lithiasis": Dr. R. J. Silvertown.
3 p.m.—Operations: Dr. R. J. Silvertown.

Wednesday, May 14.

- 4.15 p.m.—"Neoplastic Disease of the Urinary Tract": Dr. R. G. Harris.

Friday, May 16.

- 9 a.m.—"Abnormalities, Malformations and Injuries of the Urinary Tract": Dr. R. J. Silvertown.
10 a.m.—Ward rounds: Dr. R. J. Silvertown.

The fee for this course, except in the case of medical officers of the defence forces on full-time service, who are invited to attend free of charge, will be three guineas. Applications for registration, accompanied by a remittance of the fee, must be made to the Secretary, New South Wales Post-Graduate Committee in Medicine, the Prince Henry Hospital, Little Bay.

CLINICO-PATHOLOGICAL CONFERENCE.

THE next clinico-pathological conference arranged by the Post-Graduate Directors of Medicine, Surgery and Pathology will be held in the lecture hall at the Prince Henry Hospital, Little Bay, New South Wales, on Monday, March 24, 1941, at 4.30 p.m. The subjects will be cases for diagnosis and discussion: (i) a case of jaundice, (ii) a case of glycosuria.

A cordial invitation to be present is extended to all medical practitioners.

Correspondence.

ACQUIRED COLOUR VISION.

SIR: Some time since, a mariner whose colour vision had been carefully tested and found to be normal on entry into a service became grossly colour blind three years later. His form vision was well above normal. He was retired from service and given rest and was left under observation by a physician who found nothing wrong (except enlarged tonsils, which were removed). After a little more than a year he made a good recovery.

In the course of inquiry I heard of a very few similar cases. I looked up a paper by Dr. George Mackay and Dr. Dunlop, of Edinburgh, in 1898, who recorded a case of total colour blindness without loss of vision, at first without obvious cause, followed later by cerebral symptoms and death. They record the case, however, as one of acquired colour blindness in which a post-mortem examination of the brain had been made and disclosed gross cerebral lesions, secondary to carcinoma of the stomach.

The interest lies in the fact that they did not regard acquired colour blindness in itself as remarkable, and made the suggestion that a limited cerebral lesion might cause it without affecting form vision.

It is so common an experience that colour blindness is congenital that the possibility of its acquisition by unseen and unsuspected central disease or by even a toxæmia is not usually considered. But it also emphasizes the necessity for periodical examination in services in which colour vision is essential.

Yours, etc.,

JAMES W. BARRETT.

103-105, Collins Street,
Melbourne, C.1.
March 6, 1941.

Naval, Military and Air Force.

APPOINTMENTS.

THE undermentioned appointments, changes *et cetera* have been promulgated in the *Commonwealth of Australia Gazette*, Number 43, of March 6, 1941.

PERMANENT NAVAL FORCES OF THE COMMONWEALTH (SEA-GOING FORCES).

Antedating Seniority.—The seniority of Surgeon Lieutenant (D) Alan Victor Ward is antedated to 2nd December, 1939.

Termination of Appointment.—The appointment of Surgeon Lieutenant Lowen Alexander Hardy, Emergency List, for temporary service on the Active List, is terminated, dated 2nd February, 1941.

ROYAL AUSTRALIAN AIR FORCE. CITIZEN AIR FORCE.

The appointment of temporary Squadron Leader D. J. Prentice is terminated with effect from 19th February, 1941.

The following are granted commissions on probation with the rank of Flight Lieutenant, with effect from 13th February, 1941: Arthur John Mandeville Dobson, M.B., B.S.; James Francis Hughes, M.B., B.S.; and James Henry Russell Tremayne, M.D., M.R.C.P. (Lon.), M.B., B.S.—(Ex. Min. No. 36—Approved 5th March, 1941.)

Reserve.

George Brownlow Downes, M.B., Ch.M., is granted a commission on probation with the rank of Flight Lieutenant with effect from 28th January, 1941.—(Ex. Min. No. 30—Approved 5th March, 1941.)

Harry Leonard Chester, M.B., B.S., is granted a commission on probation with the rank of Flight Lieutenant with effect from 10th February, 1941.—(Ex. Min. No. 35—Approved 5th March, 1941.)

Alfred Basil Keith Watkins, M.S. (Lon.), F.R.C.S. (Eng.), L.R.C.P. (Lon.), M.B. (Lon.), is granted a commission on probation with the temporary rank of Squadron Leader, with effect from 13th February, 1941.

Obituary.

JOSEPH FRANCIS JOYCE.

We regret to announce the death of Dr. Joseph Francis Joyce, which occurred on March 10, 1941, at Ararat, Victoria.

Nominations and Elections.

THE undermentioned have applied for election as members of the New South Wales Branch of the British Medical Association:

Woolnough, Arthur Ronald, M.B., B.S., 1940 (Univ. Sydney), Sydney Hospital, Sydney.
Newton-Tabrett, Alice Eileen, M.B., B.S., 1930 (Univ. Sydney), 2, Pacific Highway, Roseville.
Thomas, Marjory Jean, M.B., Ch.M., 1918 (Univ. Sydney), 15, The Esplanade, Manly.
Goldsmith, Leslie Elmo, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.

THE undermentioned have been elected members of the New South Wales Branch of the British Medical Association:

Douglas, Raymond Lindsay, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Follett, John William, M.B., B.S., 1940 (Univ. Sydney), Royal Prince Alfred Hospital, Camperdown.
Ingils, Margaret, M.B., B.S., 1940 (Univ. Sydney), Sydney Hospital, Sydney.
Moore, Marion Hope, M.B., B.S., 1940 (Univ. Sydney), Canterbury District Hospital, Campsie.
Perkman, Salme, M.B., B.S., 1939 (Univ. Sydney), St. George District Hospital, Kogarah.
Sork, Ronald Cedric, M.B., B.S., 1940 (Univ. Sydney), Royal South Sydney Hospital, Zetland.
Rubinstein, Kusiel, M.D., 1938 (Univ. Paris), Balmmain and District Hospital, Balmmain.

THE undermentioned have applied for election as members of the South Australian Branch of the British Medical Association:

Hains, Robert Myer, M.B., B.S., 1940 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.
Wallman, Leigh Stuart, M.B., B.S., 1940 (Univ. Adelaide), 14, Balham Avenue, Kingswood.
Meredith, Mary Eva, M.B., B.S., B.Sc., 1939 (Univ. Melbourne), Northfield Infectious Diseases Hospital, Northfield.
Smith, William Arthur Rushbrook, M.B., B.S., 1939 (Univ. Adelaide), 61, East Terrace, Adelaide.

THE undermentioned have been elected a member of the South Australian Branch of the British Medical Association: Semler, Clifford Gerhardt, M.B., B.S., 1940 (Univ. Adelaide), Royal Adelaide Hospital, Adelaide.

Diary for the Month.

- MAR. 25.—New South Wales Branch, B.M.A.: Council, Quarterly.
MAR. 26.—Victorian Branch, B.M.A.: Council.
MAR. 27.—New South Wales Branch, B.M.A.: Annual.
MAR. 27.—South Australian Branch, B.M.A.: Branch.
MAR. 28.—Queensland Branch, B.M.A.: Council.
MAR. 28.—Tasmanian Branch, B.M.A.: Council.
APR. 1.—Queensland Branch, B.M.A.: Post-Graduate Committee.
APR. 1.—New South Wales Branch, B.M.A.: Council.
APR. 2.—Western Australian Branch, B.M.A.: Council.
APR. 2.—Victorian Branch, B.M.A.: Branch.
APR. 3.—South Australian Branch, B.M.A.: Council.
APR. 4.—Queensland Branch, B.M.A.: Branch.
APR. 4.—Victorian Branch, B.M.A.: Legislation Subcommittee.
APR. 8.—New South Wales Branch, B.M.A.: Organization and Science Committee.
APR. 8.—Tasmanian Branch, B.M.A.: Branch.
APR. 9.—Queensland Branch, B.M.A.: Brisbane Women's Hospital Clinical Society.
APR. 10.—Victorian Branch, B.M.A.: Ethics Committee.
APR. 15.—New South Wales Branch, B.M.A.: Executive and Finance Committee.
APR. 15.—New South Wales Branch, B.M.A.: Ethics Committee.
APR. 16.—Western Australian Branch, B.M.A.: Branch.
APR. 17.—Queensland Branch, B.M.A.: Ipswich Hospital Clinical Society.

Medical Appointments: Important Notice.

MEDICAL PRACTITIONERS are requested not to apply for any appointment mentioned below without having first communicated with the Honorary Secretary of the Branch concerned, or with the Medical Secretary of the British Medical Association, Tavistock Square, London, W.C.1.

New South Wales Branch (Honorary Secretary, 135, Macquarie Street, Sydney): Australian Natives' Association; Ashfield and District United Friendly Societies' Dispensary; Balmmain United Friendly Societies' Dispensary; Leichhardt and Petersham United Friendly Societies' Dispensary; Manchester Unity Medical and Dispensing Institute, Oxford Street, Sydney; North Sydney Friendly Societies' Dispensary Limited; People's Prudential Assurance Company Limited; Phoenix Mutual Provident Society.

Victorian Branch (Honorary Secretary, Medical Society Hall, East Melbourne): Associated Medical Services Limited; all Institutes or Medical Dispensaries; Australian Prudential Association, Proprietary, Limited; Federated Mutual Medical Benefit Society; Mutual National Provident Club; National Provident Association; Hospital or other appointments outside Victoria.

Queensland Branch (Honorary Secretary, B.M.A. House, 225, Wickham Terrace, Brisbane, B.17): Brisbane Associated Friendly Societies' Medical Institute; Proserpine District Hospital. Members accepting LODGE appointments and those desiring to accept appointments to any COUNTRY HOSPITAL, or position outside Australia are advised, in their own interests, to submit a copy of their Agreement to the Council before signing.

South Australian Branch (Honorary Secretary, 178, North Terrace, Adelaide): All Lodge appointments in South Australia; all Contract Practice appointments in South Australia.

Western Australian Branch (Honorary Secretary, 205, Saint George's Terrace, Perth): Wiluna Hospital; all Contract Practice appointments in Western Australia.

Editorial Notices.

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